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COMPOUNDS HAVING RETINOID-LIKE ACTIVITY

RELATED APPLICATIONS

This application claims the benefit under 35 U.S.C. Section 119(e) of U.S. Provisional Patent Application No. 60/269,473, filed February 16, 2001.

FIELD OF THE INVENTION

The present invention provides compounds having retinoid-like activity. More specifically, the compounds of the present invention are useful for preventing and/or treating various skin disorders, such as, but not limited to, acne, psoriasis and damage from irradiation. Further, they have antitumor and antiarthritic activities.

BACKGROUND

Retinoic acid and its natural and synthetic analogues (retinoids) exert a wide array of biological effects.
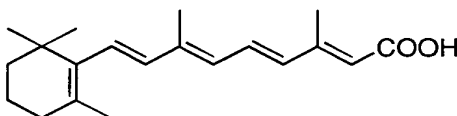
Retinoic Acid

They have been shown to affect cellular growth and differentiation and are promising drugs for the treatment of several cancers. See, for example, Roberts, A. B. and Sporn, M. B. in "The Retinoids," Sporn, *et al.* eds, 1984, 2, pp. 209-286, Academic Press, New York; Lippman, *et al.*, *Cancer Treat. Rep.*, 1987, 71, p. 391; ibid., p. 493; Hong et al., *N. Engl. J. Med.*, 1990, 323, p. 795; Huang, M. et al., *Blood*, 1988, 72, p. 567.

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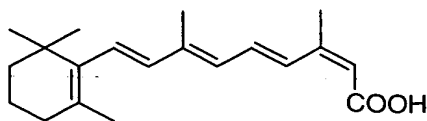
Retinoids have also been shown to be useful in treating rheumatic diseases.
See, e.g. Coffey et al., *Retinoids as Potential Antirheumatic Agents, Chemistry and*
10 *Biology of Synthetic Retinoids*, pp 520-537, CRC Press Inc., M. I. Dawson and W. H.
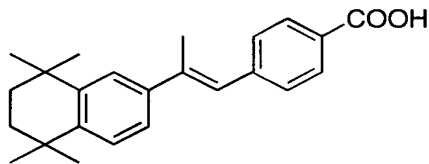Okamura Ed.(1990).

A few retinoids are already in clinical use in the treatment of dermatological
diseases such as acne and psoriasis. For example, isotretinoin is used clinically for
15 oral therapy of severe acne, and etretinate is particularly useful in the treatment of
psoriasis. *See, e.g.*, Orfanos *et al.*, Drugs, 1987, 34, pp. 459-503.
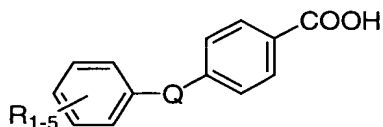
Isotretinoin

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Etretinate

I

25 II
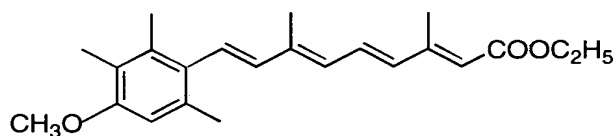
III

Other examples of retinoid compounds include arotinoid (formula II) and retinobenzoic acid (formula III), wherein Q equals --NHCO--, --CONH--, --COCH=CH--, --CH=CHCO--, --COCH₂ --, and the like. *See, e.g.* Loeliger, *et al.* *Eur. J. Med. Chem.* 1980, 15, pp. 9-15; Kagechika, H. et al., J. Med. Chem., 1988, 31, No. 11, pp. 2182-2192.

Other compounds that have been reported include:

1. European 708,100 (4/24/96), to C.I.R.D., covering the following structure:
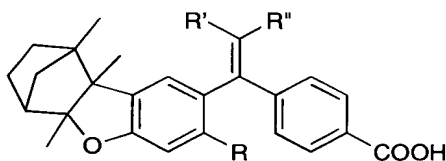
wherein R, R' and R'' are as defined therein.

2. European 709,382 (5/1/96), to C.I.R.D, covering the following structure:
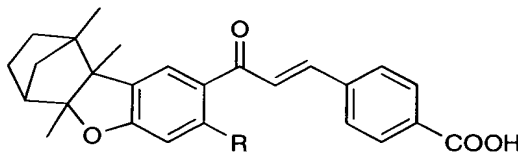
wherein R is as defined therein.

The compounds of the instant invention are distinguished from those above by the presence of a 2-atom "linker" joining the two phenyl rings, in contrast to the 1-

5 atom or 3-atom linkers shown, and by the difference in the tricyclic rings. The compounds of the instant invention contain a tricyclic fused ring system with two optionally substituted aromatic rings, rather than the tetracyclic tetrahydro-methanodibenzofuran fused ring system in the compounds shown above.

10 **SUMMARY OF THE INVENTION**

The present invention is directed to a compound having formula I:
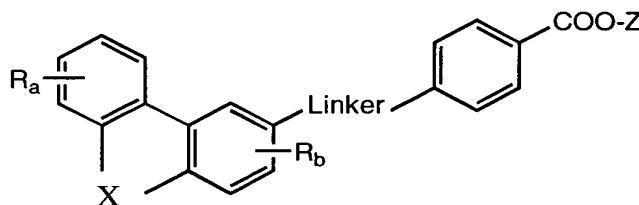
15   I

or a nontoxic pharmaceutically acceptable salt, physiologically hydrolyzable ester or solvate thereof, wherein

R_a and R_b are independently selected from the group consisting of hydrogen,
20 halogen, hydroxy, nitro, amino, substituted amino, mercapto, polyfluoroalkyl, C_{1-6} alkyl, substituted C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, formyl, carboxyl, aryl or heteroaryl;

Linker is selected from the group consisting of C_2 alkyl, C_2 alkenyl, C_2 alkynyl, --C(=O)-NH--, --NH-C(=O)--, --CH$_2$O--, --O-C(=O)--, --C(=S)--NH--,
25 --C(=O)-O--, --C(=O)-S--, --S-C(=O)--, --S-CH$_2$--, --CH$_2$-NH--, --C(=O)-CH$_2$--, --NH-C(=S)--, --CH$_2$S--, --OCH$_2$ --, --NHCH$_2$;

X is O, S, -C(R_1)$_2$-, C=O, --C(R_1)$_2$Y-- or --YC(R_1)$_2$--, wherein Y is selected from the group consisting of O, S and C(R_2)$_2$,wherein R_1 and R_2 are, independently, hydrogen or methyl; and
30 Z is hydrogen or C_{1-6} alkyl.

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5   In some embodiments, R_a and R_b are independently selected from the group
consisting of hydrogen, halogen, hydroxy, nitro, amino, mercapto, CF_3, C_{1-6} alkyl,
halosubstituted C_{1-6} alkyl, hydroxy-substituted C_{1-6} alkyl, aminosubstituted C_{1-6} alkyl,
C_{1-6} alkoxy, C_{1-6} alkylthio, formyl, carboxyl, mono- or di-C_{1-6} alkyl-substituted
amino, aryl or heteroaryl;

10   Linker is selected from the group consisting of --CH=CH--, --C≡C--, ----
C(=O)-NH--, --NH-C(=O)--, --CH$_2$O--, --O-C(=O)--, --C(=S)--NH--,
--C(=O)-O--, --C(=O)-S--, --S-C(=O)--, --S-CH$_2$--,, --CH$_2$-CH$_2$--,-CH$_2$-NH--, --
C(=O)-CH$_2$--,--NH-C(=S)--, --CH$_2$S--, --OCH$_2$ --, --NHCH$_2$ or --CRc=CRd--,
wherein Rc and Rd are independently hydrogen or C_{1-6} alkyl;

15   X is O, S, $-C(R_1)_2-$, C=O, $-C(R_1)_2Y-$ or $--YC(R_1)_2--$, wherein Y is selected
from the group consisting of O, S and $C(R_2)_2$ and R_1 and R_2 are, independently
hydrogen or methyl ; and Z is hydrogen or C_{1-6} alkyl.

        In some embodiments, X is $-C(R_1)_2Y-$ or $--YC(R_1)_2--$, wherein Y is selected
from the group consisting of O, S and $C(R_2)_2$ and R_1 and R_2 are, independently,
20   hydrogen or methyl ; and Z is hydrogen or C_{1-6} alkyl.

        In some embodiments, X is represented by O, S, $C(R_1)_2$, or C=O, wherein R_1
is hydrogen or methyl, resulting in a five-membered ring.

        In some embodiments, the present invention is directed to pharmaceutical
compositions comprising a therapeutically effective amount of the compounds of
25   formula I and a pharmaceutically acceptable carrier therefor.

DETAILED DESCRIPTION OF THE INVENTION

30   The present invention relates to compounds represented by formula I

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5   (I)

or a nontoxic pharmaceutically acceptable salt, physiologically hydrolyzable ester or

solvate thereof, wherein

10   R_a and R_b are independently selected from the group consisting of hydrogen,

halogen, hydroxy, nitro, amino, mercapto, CF_3, C_{1-6} alkyl, halosubstituted C_{1-6} alkyl,

hydroxy-substituted C_{1-6} alkyl, aminosubstituted C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio,

formyl, carboxyl, mono- or di-C_{1-6} alkyl-substituted amino, aryl or heteroaryl ;

        Linker is selected from the group consisting of --CH=CH--, --C≡C--, ----

C(=O)-NH--, --NH-C(=O)--, --CH$_2$O--, --O-C(=O)--, --C(=S)--NH--, --C(=O)-O--,

15   --C(=O)-S--, --S-C(=O)--, --S-CH2--,, --CH2--CH2--,-CH2-NH--, --C(=O)-CH2--,

--NH-C(=S)--, --CH2S--, --OCH2 --, --NHCH2-- or CRc=CRd--, where Rc and Rd are

independently hydrogen or C_{1-6} alkyl;

        X is –C(R)$_2$Y-- or --YC(R)$_2$--, where Y is selected from the group consisting

of O, S and C(R)$_2$; or

20   X is selected from the group consisting of O, S, C(R)$_2$, and C=O (5-membered ring),

wherein R is hydrogen or methyl; and

        Z is hydrogen or C_{1-6} alkyl.

Definitions

        As used herein, the term "alkyl" includes cyclic, branched and straight chain

25   saturated aliphatic hydrocarbon groups having the specified number of carbon atoms,

such as methyl, ethyl, propyl, isopropyl, butyl, sec and tert-butyl, pentyl, hexyl,

heptyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, 2-

methylcyclopropyl, cyclopropylmethyl, octyl, nonyl,

norbornyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, eicosyl, 3,7-diethyl-2,2-

30   dimethyl-4-propylnonyl, cyclododecyl, adamantyl, and

5   the like. Alkyl groups may be substituted with substituents, such as, halo, amino, hydroxy, alkoxy, cycloalkoxy, heterocyclooxy, alkylamino, arylamino, aralkylamino, cycloalkylamino, heterocycloamino, disubstituted amines in which the 2 amino substituents are selected from alkyl, aryl or aralkyl; alkanoylamino, aroylamino, aralkanoylamino, substituted alkanoylamino, substituted

10   arylamino, substituted aralkanoylamino, thiol, alkylthio, arylthio, aralkylthio, cycloalkylthio, heterocyclothio, alkylthiono, arylthiono, aralkylthiono, alkylsulfonyl, arylsulfonyl, aralkylsulfonyl, sulfonamido, e.g. SO_2NH_2, substituted sulfonamido, nitro, cyano, carboxy, carbamyl, e.g. $CONH_2$, substituted carbamyl e.g. CONH alkyl, CONH aryl, CONH aralkyl or

15   cases where there are two substituents on the nitrogen selected from alkyl, aryl or aralkyl; alkoxycarbonyl, aryl, substituted aryl, guanidino and heterocycles, such as, indolyl, imidazolyl, furyl, thienyl, thiazolyl, pyrrolidyl, pyridyl, pyrimidyl and the like.

The term "polyfluoroalkyl" means that at least one hydrogen atom in an alkyl

20   side-chain is replaced by a fluorine atom.

The term "amino", herein alone or as part of another group refers to $-NH_2$. An "amino" may optionally be substituted with one or two substituents, which may be the same or different, such as alkyl, aryl, arylalkyl, alkenyl, alkynyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, cycloalkyl, cycloalkylalkyl,

25   haloalkyl, hydroxyalkyl, alkoxyalkyl or thioalkyl. These substituents may be further substituted with a carboxylic acid or any of the alkyl or aryl substituents set out herein.

The term "alkenyl" defines a carbon chain having at least one double bond. For example, C_{2-6} alkenyl refers to a straight or branched chain of two to six carbons

30   bearing at least one double bond, such as ethenyl, 1-methyl-ethenyl, 1- or 2-propenyl, 1-methyl-1-propenyl, 1-methyl-2-propenyl, 1,1-dimethyl-2-propenyl, 2-methyl-2-propenyl, 1- , 2- or 3-butenyl, 1-methyl-1-butenyl, 2-methyl-1-butenyl, 3-methyl-1-butenyl, 3,3-dimethyl-1-butenyl, 1,2,3-dimethyl-1-butenyl, 1-methyl-2-butenyl, 1,1-dimethyl-2-butenyl, 2-methyl-2-butenyl, 3-methyl-2-butenyl, 1,3-butadienyl, 1,3-

35   dimethyl-1,3-butadienyl, 1-, 2-, 3- or 4-pentenyl and the like. Alkenyl groups may be substituted with groups such as halo, alkoxy, cycloalkoxy, heterocyclooxy, arylamino,

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5   , heterocycloamino, disubstituted amines in which the 2 amino substituents are

selected from alkyl, aryl or aralkyl; alkanoylamino, aroylamino, aralkanoylamino,

substituted alkanoylamino, substituted arylamino, substituted aralkanoylamino,

alkylthio, arylthio, aralkylthio, cycloalkylthio, heterocyclothio, alkylthiono,

arylthiono, aralkylthiono, alkylsulfonyl, arylsulfonyl, aralkylsulfonyl,

10   sulfonamido, e.g. SO_2NH_2, substituted sulfonamido, nitro, cyano, carboxy, carbamyl,

e.g. $CONH_2$, substituted carbamyl e.g. CONH alkyl, CONH aryl, CONH aralkyl or

cases where there are two substituents on the nitrogen selected from alkyl, aryl or

aralkyl; alkoxycarbonyl, aryl, substituted aryl, guanidino and

heterocycles, such as, indolyl, imidazolyl, furyl, thienyl, thiazolyl, pyrrolidyl, pyridyl,

15   pyrimidyl and the like.

The term "alkynyl" defines a carbon chain having at least one triple bond. For

example, C_{2-6} alkynyl refers to a straight- or branched-chain of two to six carbons

bearing at least one triple bond, such as ethynyl, 1- or 2-propynyl, 1-methyl-2-

propynyl, 1,1-diemthyl-2-propynyl, 1-, 2- or 3-butynyl, 3-methyl-1-butynyl, 3,3-

20   dimethyl-1-butynyl, 1-methyl-2-butynyl, 1,1-dimethyl-2-butynyl, 1-, 2-, 3, or 4-

pentynyl and the like.

The term "C_{3-6} cycloalkyl" refers to cyclopropyl, cyclobutyl, cyclopentyl or

cyclohexyl radicals.

The terms "C_{1-6} alkoxy" and "C_{1-6} alkylthio" refer to an ether or a thioether

25   bearing a straight or branched carbon chain, such as methoxy, methylthio, ethoxy,

ethylthio, n-propoxy, n-propylthio, isopropoxy, isopropylthio, n-butoxy, n-butylthio,

tert-butoxy, tert-butylthio, n-pentoxy, n-pentylthio and the like. The terms "halogen"

or "halo" refer to fluorine, chlorine, bromine or iodine. The term "aryl" as used

herein and in the text includes mono-, bi- and polycyclic aromatic groups such as

30   phenyl, naphthyl, anthracyl, phenanthryl, biphenyl, binaphthyl and the like.

The term "heteroaryl" as used herein includes mono-, bi- and polycyclic

aromatic heterocyclic groups containing 1 to 4 O, N or S atoms: preferred are 5- and

6-membered heterocyclic groups such as thienyl, furyl, thiadiazolyl, oxadiazolyl,

triazolyl, isothiazolyl, thiazolyl, imidazolyl, isoxazolyl, tetrazolyl, oxazolyl, pyridyl,

35   pyrazinyl, pyrimidinyl, pyridazinyl, pyrrolyl, pyrazolyl, and the like and fused 5,6-

membered and 6,6-membered heterocyclic groups such as benzofuranyl,

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5   isobenzofuranyl, benzothienyl, indolyl, isoindolyl, indazolyl, indolizinyl, iosquinolyl, quinolyl, naphthyridinyl, quinoxalinyl, quinazolinyl, pteridinyl and the like.

Some compounds represented by formula I may also form pharmaceutically acceptable metal and amine salts in which the cation does not contribute significantly to the toxicity or biological activity of the salt. These salts are also part of the present

10   invention. Suitable metal salts include the sodium, potassium, calcium, barium, zinc, and aluminum salts. The sodium or potassium salts are preferred. Amines which are capable of forming stable salts with the compounds represented by formula I include trialkylamines such as triethylamine, procaine, dibenzylamine, N-benzyl-β-phenethylamine, 1-ephenamine, N,N'-dibenzylethylene-diamine,

15   dehydroabietylamine, N-ethylpiperidine, benzylamine, dicyclohexylamine or other pharmaceutically acceptable amines.

Since compounds of formula I contain a carboxy group, they can form physiologically hydrolyzable esters which serve as prodrugs by being hydrolyzed in the body to yield formula I compounds *per se*. They are preferably administered

20   orally since hydrolysis in many instances occurs principally under the influence of the digestive enzymes. Parenteral administration may be used where the ester *per se* is active, or in those instances where hydrolysis occurs in the blood. Examples of physiologically hydrolyzable esters of compounds of formula I include C_{1-6} alkyl benzyl, 4-methoxybenzyl, indanyl, phthalilyl, methoxymethyl, C_{1-6} alkanoyloxy-C_{1-6}

25   alkyl, e.g. acetoxymethyl, pivaloyloxymethyl or propionyloxymethyl, C_{1-6} alkoxycarbonyloxy-C_{1-6} alkyl, e.g. methoxycarbonyloxymethyl or ethoxycarbonyloxymethyl, glycyloxymethyl, phenylglycyloxymethyl, (5-methyl-2-oxo-1,3-dioxolen-4-yl)-methyl and other well known physiologically hydrolyzable esters used, for example, in the penicillin and cephalosporin arts. Such esters are

30   prepared by conventional techniques known in the art.

The structural formulae as drawn in the instant application are believed to best represent the structures of compounds of the present invention. However, some compounds within the scope of the invention may exist as other tautomeric forms, in which hydrogen atoms are transposed to other parts of the molecules and the chemical

35   bonds between the atoms of the molecules are consequently rearranged. It should be

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5   understood that the structural formulae represent all tautomeric forms, insofar as they may exist.

Some of the compounds of the present invention may have *trans* and *cis* (E and Z) isomers. In addition, the compounds of the present invention may contain one or more chiral centers and therefore may exist in enantiomeric and diastereomeric

10   forms. The scope of the present invention is intended to cover all such isomers per se, as well as mixtures of *cis* and *trans* isomers, mixtures of diastereomers and racemic mixtures of enantiomers (optical isomers). In the present application, when no specific mention is made of the configuration (*cis*, *trans* or R or S) of a compound (or of an asymmetric carbon) then a mixture of such isomers, or either one of the isomers

15   is intended.

As used herein and in the reaction schemes, the term "Grignard type reaction" is intended to include the addition of an organometallic compound to a carbonyl-containing compound. This includes addition of Grignard reagents, alkyl or aryllithiums, alkylzinc, alkylaluminum, organotitanium, organozirconium or

20   organocerium compounds in an inert organic solvent such as ethyl ether, tetrahydrofuran, dichloromethane, benzene or toluene and the like. In certain instances, the complexation of the ketone or the Grignard reagent with cerium halides, perchlorate salts or tetraalkylammonium halides is necessary to improve the addition reaction. The term "Grignard type reaction" is also intended to include the addition of

25   a Grignard reagent to an acid chloride that has been first reacted with tributylphosphine to form the corresponding phosphonium salt. The reaction is performed in an inert organic solvent such as ethyl ether, tetrahydrofuran, benzene and the like.

As used herein and in the reaction schemes, the term "Friedel-Crafts reaction"

30   is intended to include the acylation or alkylation of aromatic rings. The acylation includes the addition of an acyl halide, a carboxylic acid, an anhydride or a ketene to an aromatic ring under Lewis acid conditions such as aluminum, tin, antimony, zirconium, or boron halides and the like or under proton acid conditions such as polyphosphoric acid, sufluric acid, methanesulfonic acid and the like. The alkylation

35   includes the addition of alkyl halides, olefins or alcohols under Lewis or proton acid conditions such as those listed above.

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5   The term "aromatic halogenation" is intended to include the addition of chlorine, bromine or iodine to an aromatic ring in presence or absence of a catalyst, usually iron or a Lewis acid such as aluminum, tin, or antimony halides and the like. It is also intended to include the reaction of N-chloro and N-bromoamides catalyzed by the addition of acids. For iodination, iodine may be used in the presence of an

10   oxidizing agent such as nitric acid, iodic acid, sulfur trioxide or hydrogen peroxide or in the presence of copper salts, silver trifluoromethanesulfonate or thallium(I) acetate. Iodine monochloride can also be used.

The term "reduction" is intended to include well-known reduction procedures of ketone groups by the use of aluminum or

15   boron hydrides such as lithium aluminum hydride, aluminuim hydride, diisobutylaluminum hydride, sodium borohydride, sodium cyanoborohydride and the like in an inert organic solvent such as tetrahydrofuran, ethyl ether, ethanol, dichloromethane and the like. The term "reduction" is also intended to include the reduction or desulfurization of dithioacetals by the use of Raney nickel with or

20   without hydrogen in organic solvents such as methanol, ethanol, ethanol/water, ethanol/ethyl ether, dioxane, acetone, tetrahydrofuran benzene and the like. Other conditions to perform hydrogenolysis are the use of trialkyltin hydrides in the presence of AIBN in an inert organic solvent such as benzene or toluene, or the use of aluminum or boron hydride such as lithium aluminum hydride or sodium borohydride

25   in the presence of titanium(IV) chloride or nickel(II) chloride in tetrahydrofuran, ethanol or dimethylformamide.

The term "reduction" is also intended to include well-known reduction procedures of benzylic alcohols. These methods include the use of aluminum, boron or trialkylsilyl hydrides such as lithium aluminum hydride, sodium borohydride,

30   sodium cyanoborohydride or triethylsilylhydride with or without aluminum chloride, zinc iodide or an acid such as hydrochloric acid, trifluoroacetic acid or trifluoroboron etherate in an inert organic solvent such as tetrahydrofuran, ethyl ether or ethanol. Well-known hydrogenolysis procedures using hydrogen with a catalyst such as palladium on charcoal or Raney nickel in methanol, or ethanol may also be used if

35   appropriate.

5   As used herein and in the reaction schemes, the term "reductive amination" is

intended to include conventional imine formation procedures well-known to those

skilled in the art. These procedures involve the reaction of an amine with a Lewis

acid such as titanium(IV) chloride or isopropoxide. Subsequently, this imine is

reduced with well-known reductive agents such as sodium borohydride or sodium

10   cyanoborohydride.

As used herein and in the reaction schemes, the term "hydrolysis" is intended

to include conventional hydrolysis procedures of esters well-known to those skilled in

the art. For example, methyl or ethyl esters may be removed by the use of aqueous

solutions of sodium or potassium alkoxides in tetrahydrofuran or ethanol. The

15   hydrolysis of tert-butyl esters are carried out under acidic conditions such as 90%

trifluoroacetic acid or 6N hydrochloric acid in solvents such as tetrahydrofuran or

dichloromethane. Allyl esters may be removed by the use of Pd(0) catalyst such as

sodium acetate, potassium or sodium 2-ethylhexanoate, pyrolidine or morpholine and

the like in an organic solvent such as acetonitrile, tetrahydrofuran, dichloromethane

20   and the like. Finally, silyl esters such as trimethylsilylethyl esters may be cleaved by

the use of tetrabutylammonium fluoride in tetrahydrofuran. The term "hydrolysis" is

also intended to include conventional hydrolysis procedures of carbonyl protecting

groups. For example, the hydrolysis of ketals and acetals may be carried out under

acidic conditions such as 1N hydrochloric acid, 80% acetic acid or p-toluenesulfonic

25   acid in solvents such as tetrahydrofuran or acetone.

As used herein and in the reaction schemes, the term "enol triflate or enol

formation" is intended to include conventional and well-known enolate formation

procedures and subsequent trapping of this enolate by the well-known triflating or

silylating agents. Thus the ketones are treated with an organic base such as 2,6-di-

30   tert-butyl-4-methyl-pyridine, sodium hydride, potassium hydride, lithium

diisopropylamide or lithium bis(trimethylsilyl)amide in an inert organic solvent such

as tetrahydrofuran, dimethylformamide or dichloromethane and the like. The

resulting enolates are then reacted with triflic anhydride or 2-[N,N-

bis(trifluoromethylsulfonyl)amino]pyridine and the like or an alkylsilyl halide or

35   triflate.

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5   As used herein and in the reaction schemes, the term "cross-coupling" is
intended to include all the cross-coupling methods well-known by those skilled in the
art that involve the reaction of a vinyl or aromatic triflate, bromide or iodide with a
tin, zinc, magnesium or boronic derivative catalyzed by a palladium(0) or
palladium(II) catalyst such as tetrakis(triphenyl-phosphine)palladium(0),

10   bis(triphenylphosphine)palladium(II) chloride, palladium(II) acetate,
tris(dibenzylidene-acetone)dipalladium(0),
bis(diphenylphosphineferrocene)palladium(II) chloride and the like or a nickel(0) or
nickel(II) catalyst such as tetrakis(triphenylphosphine)nickel(0),
bis(triphenylphosphine)nickel(II) chloride and the like. Very often, as known by

15   those skilled in the art, copper iodide, lithium chloride, zinc chloride or
triphenylarsine, tris(2-furyl)phosphine or tris(2,4,6-trimethoxyphenyl)phosphine must
be added. When a boronic acid derivative is used, the reaction proceeds only in the
presence of an inorganic base such as potassium phosphate or carbonate or sodium
carbonate. These reactions are performed in an inert organic solvent such as dioxane,

20   N-methylpyrrolidone, dimethylformamide, dimethoxyethane, tetrahydrofuran,
toluene, benzene and the like.

        As used herein and in the reaction schemes, the term "Heck coupling" is
intended to include all known vinylations of alkenes or alkynes. Thus, a vinyl or
aromatic triflate, bromide or iodide reacts with various substituted or non-substitued

25   alkenes or alkynes in the presence of a trialkylamine base or an inorganic base such as
potassium carbonate, sodium acetate and the like and a catalytic amount of Pd(II)
complex such as palladium(II) acetate, bis(triphenylphosphine)palladium(II) chloride
or bis(acetonitrile)palladium(II) chloride. Sometimes phosphine ligands such as
triphenylphosphine, tritolylphosphine, diphenylphosphineferrocene or 1,3-

30   bis(diphenylphosphino) propane and the like may facilitate the reaction.

        As used herein and in the reaction schemes the term "alkylation" is intended to
include conventional and well-known alkylation procedures. Thus, the desired
alcohol or ketone groups which are to be alkylated are treated in the presence of an
organic or inorganic base such as sodium hydride, potassium hydride, lithium

35   diisopropylamine or lithium bis(trimethylsilyl)amide in an inert organic solvent such
as tetrahydrofuran, dimethylformamide, hexamethylphosphoramide,

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5   dimethylsulfoxide, N-methylpyrolidinone and the like. Then an alkylating agent such
as an alkyl, allyl or benzyl halide, mesylate or tosylate is added to this generated
enolate, phenolate or thiophenolate. As used herein and in the reaction schemes the
term "reductive alkylation" is intended to include the methods used to convert a
tertiary alcohol to an alkyl, aryl or allyl group. Thus, the alcohol that has to be
10   transformed may be treated by an organosilicon compound in the presence of boron
trifluoride in dichloromethane or by a trialkylboron in the presence of
trifluoromethanesulfonic acid in 1,1,2-trichlorotrifluoroethane. Another method is to
react the corresponding alkoxide with iron pentacarbonyl to perform a deoxygenation
reaction which may be worked-up by various alkyl or aryl halides. The alkoxide may
15   be generated by treatment with a metal such as potassium, sodium or lithium in
toluene.

As used herein and in the reaction schemes the term "oxidation" is intended to
include conventional allylic oxidation methods such as selenium dioxide with or
without the use of tert-butyl peroxide, sodium peroxide in ethanol and chromium(VI)
20   reagents such as chromium(VI) trioxide in acetic acid and pyridinium dichromate and
preferably potassium bromate in presence of ceric ammonium nitrate in dioxane.

As used herein and in the reaction schemes the term "aromatic substitution" is
intended to include, in addition to the classic electrophilic reactions, nucleophilic
substitutions of aromatic halides by water in the presence of sulfuric acid or
25   trifluoroacetic acid, by alkoxides, aryloxides, thioalkoxides or thioaryloxides in an
inert organic solvent such as hexamethylphosphoramide, dimethylsulfoxide,
dimethylformamide and the like. The reaction of aryl halides with alkoxides may be
promoted by copper salts and the reaction with thioalkoxides may be catalyzed by
Pd(0) salts such as tetrakis(triphenylphosphine)palladium(0).

30   As used herein and in the reaction schemes the term "enone formation" is
intended to include the well-known dehydrogenation procedures of ketones.
Preferably, the ketone to be dehydrogenated is converted to a silyl enol ether as
described above and then treated with an oxidizing agent such as
dichlorodicyanoquinone, triphenylmethylcation or palladium(II) acetate in an inert
35   organic solvent such as acetonitrile or dichloromethane.

5   As used herein and in the reaction schemes, the term "Michael addition" is
intended to include all conventional methods of conjugate addition of organometallic
compounds or anions formed from malonates, cyanoacetates, acetoacetates, β-
ketoesters, esters, ketones, alkehydes, nitriles, nitro compounds, sulfones and the like
to an α,β-unsaturated ketone. The organometallic compounds include lithium

10   dialkylcopper, organoaluminum, trialkylzinc lithium, arylpalladium, arylmercury,
borane reagents and the like. The inert organic solvents used may be tetrahydrofuran,
dioxane, dimethylformamide, dichloromethane, benzene and the like.

As used herein and in the reaction schemes, the term "acid halide formation" is
intended to include the well-known methods of the conversion of a carboxylic acid to

15   an acid halide such as the use of thionyl chloride, oxalyl chloride or bromide in
presence of dimethylformamide in dichloromethane and phosphorus trichloride or
tribromide.

As used herein and in the reaction schemes, the term "Wittig type reaction" is
intended to include conventional methods of Horner-Emmons, Nysted or Wittig

20   olefination reactions of aldehydes or ketones. Thus, in a Horner-Emmons olefination,
an alkyl or aryl phosphonate is treated with a base such as sodium hydride, lithium
diisopropylamide or lithium bis(trimethylsilyl)amide and the like in an inert organic
solvent such as tetrahydrofuran, dichloromethane, benzene and the like and reacted
with a ketone or an aldehyde. In a Wittig reaction, an alkyl or arylphosphonium salt

25   is treated with a base such as butyllithium, lithium diisopropylamine or lithium
bis(trimethylsilyl)amide and the like in an inert organic solvent such as
tetrahydrofuran, dichloromethane, benzene and the like and reacted with a ketone or
an aldehyde. In a Nysted olefination, the ketone is treated with {cyclo-dibromodi-μ-
methylene[μ-(tetrahydrofuran)]trizinc} (Nysted reagent) in the presence of titanium

30   chloride in an inert solvent such as tetrahydrofuran and dichloromethane.

As used herein and in the reaction schemes, the term "epoxidation or
thioepoxidation" is intended to include the well-known methods of epoxide formation
by reaction of an olefin with a per-acid as well as epoxide formation by reacting a
gem-dihalide in presence of a strong base such as butyllithium, t-butyllithium

35   methyllithium or lithium with a ketone in inert organic solvents such as
tetrahydrofuran or ether. It is also intended to include methods using the reaction of

5   sulfur ylides such as dimethyloxosulfonium methylide and dimethylsulfonium methylide which are generated by treatement of the corresponding sulfonium salt with an organic base such as sodium hydride or potassium tert-butoxide in organic solvents such as dimethylsulfoxide, tetrahydrofuran, t-butanol, dimethoxyethane and the like with a ketone. The term "epoxidation or thioepoxidation" is also intended to include

10   the methods by which a diazoalkane reacts with a ketone in solvent such as methanol or ethyl ether.

As used herein and in the reaction schemes, the terms "acetal, ketal, thioacetal or thioketal formation" are intended to include processes well-known in the art and they are well illustrated in "Protective Groups in Organic Synthesis", Second Ed., T.

15   W. Green and P. G. W. Wuts, John Wiley & Sons, New York, 1991, Chapter 4 and references therein. Thus, the ketone or aldehyde that has to be reacted is treated with the desired alcohol or diol, thiol or dithiol in the presence of an inorganic or organic acid such as p-toluenesulfonic acid, hydrochloric acid, trifluoroboron etherate, oxalic acid, adipic acid, pyridinium tosylate, acetic acid and the like, in inert organic

20   solvents such as benzene, toluene, acetonitrile or dichloromethane.

As used herein and in the reaction schemes, the term "cyclopropanation" is intended to include the well-known Simmons-Smith procedure involving the reaction of a dihaloalkane and zinc-copper couple with an olefin in organic solvents such as ethyl ether, dimethoxyethane or tetrahydrofuran. The preparation of the zinc-copper

25   couple is preferably carried out with zinc dust and cuprous chloride. Other variations of this procedure are the use of a dihaloalkane with samarium, mercuric chloride in tetrahydrofuran or with diethylzinc in dichloromethane or toluene. The term "cyclopropanation" is also intended to include the addition of carbenes to double bonds such as the reaction of a diazoalkane with rhodium acetate or palladium(II)

30   acetate in tetrahydrofuran or dichloromethane, the reaction of a dihaloalkane with a strong base such as n-butyllithium, methyllithium or t-butyllithium in inert organic solvents such as ethyl ether or tetrahydrofuran or the reaction of chloroform with sodium or potassium hydroxide under phase transfer conditions such as tetraalkylammonium halide in water or a mixture of water/ethanol.

35   The term "imine formation" is intended to include the well-known procedures by which a ketone reacts with an amine in presence of an acid with or without a

16

5   drying agent. These conditions include various inorganic and organic acids such as zinc chloride, titanium chloride, hydrochloric acid, sulfuric acid, trifluoroacetic acid, acetic acid, p-toluenesulfonic acid and the like in solvents such as dichloromethane, ethanol, benzene, toluene, tetrahydrofuran, dimethylformamide and the like.

10   Modes of Administration

The compounds of this invention may be administered systemically or topically, depending on the condition to be treated, the need for site-specific treatment or the quantity of drug to be administered.

In the treatment of skin-related diseases such as acne, it will generally be

15   preferred to administer the drug topically, although oral administration may also be used for the treatment of severe acne or psoriasis. In the treatment of cancerous or precancerous conditions, the drug is preferably administered systemically.

The topical formulation used may be a solution, suspension, gel or ointment and the like. If the drug is to be administered systemically, it may be prepared as a

20   powder, pill, tablet or the like or as a syrup suitable for oral administration. For intravenous or intraperitoneal administration, the compound will be prepared as a solution or suspension capable of being administered by injection.

Treatment of skin-related diseases or cancerous and precancerous conditions will be effected by administration of the therapeutically effective dose of one or more

25   compounds of the present application. A therapeutic concentration will be the concentration which effects reduction of the condition or retards its expansion.

The compounds of formula I above may be used topically or systemically, as anticancer agents and in the treatment, amelioration or prevention of the skin disorders and rheumatic illnesses, such as, osteorarthritis, treatment of transplant

30   rejections, psoriasis, psoriatic arthritis, inflammatory bowel disease, acute pancreatitis, and chronic pancreatitis (including rheumatoid arthritis) as described in U.S. Pat. No. 5,618,839. In this regard they may be used for therapy in animals, including humans, of premalignant epithelial cell lesions, as a prophylaxis against tumor promotion in epithelial cells and treatment for dermatoses such as ichthyoses,

35   follicular disorders, benign epithelial disorders and other proliferative skin diseases such as psoriasis, eczema, atopic dermatitis, non-specific dermatosis and the like.

17

5   They may also be used in reversing and preventing the effects of irradiation damage

to skin. When used for the above purposes, they will usually be formulated with a

pharmaceutically acceptable liquid, semi-solid, or solid carrier. A pharmaceutically

acceptable carrier is a material that is nontoxic and generally inert and does not

adversely affect the functionality of the active ingredients. Such materials are well

10   known and include those materials sometimes referred to as diluents or vehicles

(excipients) in the pharmaceutical formulation art. The carrier may be organic or

inorganic in nature.

Examples of pharmaceutically acceptable carriers that may be used to

formulate a compound of formula I are water, gelatin, lactose, starch, mineral oil,

15   cocoa butter, dextrose, sucrose, orbital, mannitol, gum acacia, alginates, cellulose,

talc, magnesium stearate, polyoxyethylene sorbitan monolaurate, and other commonly

used pharmaceutical carriers. In addition to a compound of formula I and carrier, the

formulation may contain minor amounts of additives such as flavoring agents,

coloring agents, thickening or gelling agents, emulsifiers, wetting agents, buffers,

20   stabilizers, and preservatives such as antioxidants.

The dosages and dosage regimen in which the compounds of formula I are

administered will vary according to the dosage form, mode of administration, the

condition being treated and particulars of the patient being treated. Accordingly,

optimal therapeutic concentrations will be best determined at the time and place

25   through routine experimentation.

In the treatment of dermatoses, it will generally be preferred to administer the

drug topically, though in certain cases oral administration may also be used. If the

compounds according to the invention are used topically, it will be found that they

exhibit a good activity over a very broad range of dilution; in particular,

30   concentrations of the active compound or compounds ranging from 0.0005% to 2%

by weight can generally be used. It is of course possible to use higher concentrations

if this should become necessary for a particular application; however, the preferred

concentration of active principle are from 0.002% to 1% by weight.

For topical administration the compounds of formula I are conveniently

35   provided in the form of unguents, gels, creams, ointments, powders, dyeing

compositions, solutions, suspension, emulsions, lotions, sprays, adhesive plasters and

5   impregnated pads. The compounds according to the invention can be mixed with inert nontoxic, generally liquid or pasty, bases suitable for topical treatment. Preparation of such topical formulations are well described in the art of pharmaceutical formulations as exemplified, for example, Remington's Pharmaceutical Science, Edition 17, Mack Publishing Company, Easton, Pa. Other medicaments can be added to such

10   formulation for such secondary purposes as treating skin dryness, providing protection against light; other medications for treating dermatoses, preventing infection, reducing irritation, inflammation and the like.

        The compounds according to the invention can also be used enterally. Orally, the compounds according to the invention are suitable administered at the rate of 100

15   μg to 100 mg per day per kg of body weight. The required dose can be administered in one or more portions. For oral administration, suitable forms are, for example, tablets, pills, dragees, syrups, suspensions, emulsions, solutions, powders and granules; a preferred method of administration consists in using pills containing from 1 mg to about 1000 mg of active substance.

20   U.S. Pat. No. 4,876,381 issued on Oct. 24, 1989 to Lang et al. provides examples of formulations constituting gel, unguent, powder, cream, and the like. The aforesaid U.S. patent can be used as a guide to formulate a compound of formula I and is herein incorporated by reference in its entirety.

        Several retinoids have been found to possess anti-tumor properties. See, for

25   example, Roberts, and Sporn, in "The Retinoids", Sporn, M. B., Roberts, A. B., and Goodman, D. S., eds, 1984, 2 pp. 209-286, Academic Press, New York; Lippman, et al. *Cancer Treat. Rep.*, 1987, 71, p. 391; ibid., p. 493.

        As used herein, the term "anti-tumor" includes both chemopreventive (prophylactic or tumor promotion inhibiting) and therapeutic (curative) use. For

30   example, all-trans retinoic acid can be used to treat acute promyelocytic leukemia. See, for example, Huang, et al., *Blood*, 1988, 72 p. 567. Isotretinoin has been shown to be useful in prevention of second primary tumors in squamous-cell carcinoma of the head and neck. Hong, W. K. et al., N. Engl. J. Med., 1990, 323 p. 795.

        The compounds of formula I can be used in a substantially similar manner to

35   other retinoids for treating (both chemopreventively and therapeutically) various tumors. For the compounds of this invention, the anti-tumor dose to be administered,

5   whether a single dose, multiple dose, or a daily dose, will of course vary with the

particular compound employed because of the varying potency of the compound, the

chosen route of administration, the size of the recipient, the type of tumor, and the

nature of the patient's condition. The dosage to be administered is not subject to

definite bounds, but it will usually be an effective amount, or the equivalent on a

10   molar basis of the pharmacologically active free form produced from a dosage

formulation upon the metabolic release of the active drug to achieve its desired

pharmacological and physiological effects. An oncologist skilled in the art of cancer

treatment will be able to ascertain, without undue experimentation, appropriate

protocols for the effective administration of the compounds of this present invention,

15   such as by referring to the earlier published studies on retinoids found to have anti-

tumor properties. For example, for the prevention of second primary tumors with a

compound of formula I in squamous-cell carcinoma of the head and neck, an

oncologist may refer to the study by Hong, et al. in *N. Engl. J. Med.*, 1990, 323, p.

795. For treating acute promyelocytic leukemia, the oncologist may refer to the study

20   by Huang, *et al. in Blood*, 1988.

Compounds of the present invention are useful for the minimization or

prevention of post-surgical adhesion formation between organ surfaces. The term

"organ surface" is intended to encompass any internal organ of a living animal.

including but not limited to the uterus, intestines, liver, kidneys, heart and lungs.

25   For prevention of surgical adhesions, the compounds may be administered by a

variety of systemic and local methods. The compounds may be administered orally,

by intravenous injection, by intramuscular injection or by intracavity instillation. The

general range of doses will depend on the efficacy of each compound and the intended

route but is expected to be from 0.1 mg/kg to 100 mg/kg. Preferred routes of

30   administration are oral administration or direct administration (intracavity instillation)

to a site of surgical activity on an organ surface. For intracavity administration the

retinoid can be administered in a suitable vehicle such as 5% dextrose in water

adjusted to a pH to assure complete salt formation. However it is understood that

many other single dose delivery systems could be contemplated by those skilled in the

35   art including microcapsules, microspheres, liposomes, viscous instilates, and

polymeric delivery materials. U.S. Pat. No. 6,319,948, incorporated herein by

5   reference, describes the use of retinoid-like compounds for the treatment of post-
surgical adhesion formation.

      The synthesis of a compound of formula I can be accomplished by a wide
variety of methods using conventional starting materials and processes. The synthetic
descriptions and specific examples that follow are only intended for the purpose of

10   illustration, and are not to be construed as limiting in any manner ways to make
compounds of the present invention by other methods.

      Typically a compound of formula I can be made by employing one of the
processes or obvious variations thereof as depicted in Schemes I to III. All the steps in
Schemes I to III are standard processes which can be easily practiced by anyone

15   skilled in the art. The specific examples that are provided after the Schemes are
intended to illustrate specific conditions which may be employed to carry out certain
steps in the Schemes and are not to be construed as limiting the conditions in any
way.

20   Synthetic routes:

1   2   3

4a   4b   5

21
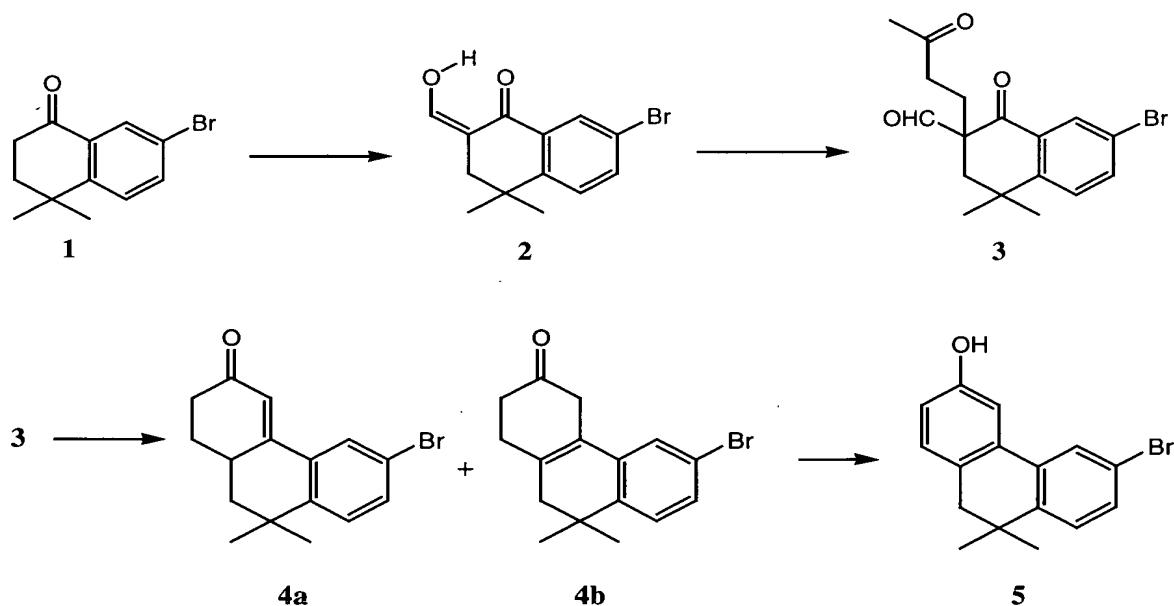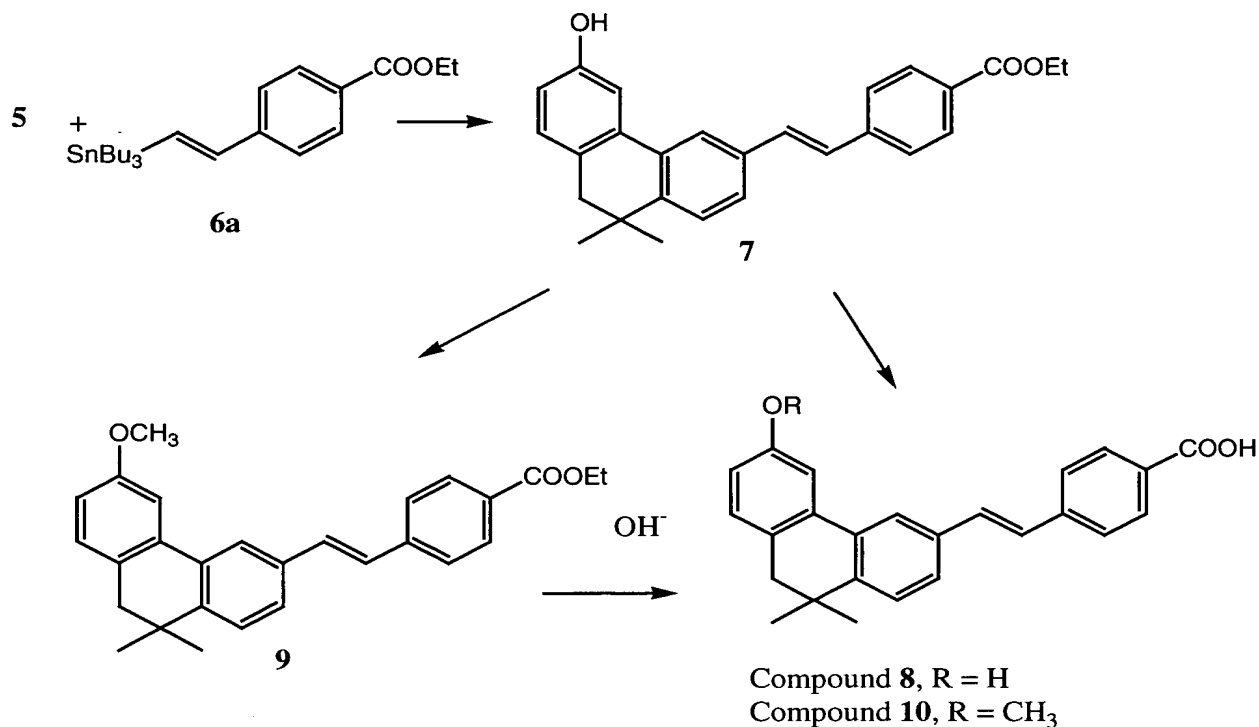
Scheme I

Compounds **8** and **10**, where **X** = -CH₂C(CH₃)₂- , R = H (compound 8) or CH₃

(compound 10) and Linker = -CH=CH- , may be synthesized as shown in Scheme I.

Known bromo-tetralone **1** (from J. Starrett *et al*; European patent application

#661,259 (7/5/95) or Y. Endo *et al*; *J Med Chem* 1998, *41*, 1476-96) may be

formylated, using, for example, ethyl formate in the presence of sodium hydride base

in a suitable solvent such as benzene, to give hydroxymethylene compound **2**.

Compound **2** may be condensed under basic conditions with methyl vinyl ketone to

give annulated derivative **3**. **3** may then undergo a hydroxide-catalyzed ring closure

and side-chain hydrolysis to give the mixture of enones **4a** + **4b**. This mixture may

then be aromatized at elevated temperature in the presence of a catalyst such as

palladium chloride to give aromatized compound **5**. **5** may undergo a Stille-type

coupling with **6a** to give ester **7**, which can either be hydrolyzed directly to give final

compound **8** or reacted with an alkylating agent such as methyl iodide to give the

ether **9**, which may then be hydrolyzed to give final compound **10**. Similar

5   compounds where Linker = -C≡C- may be synthesized by substituting reagent **6b** for

6a in the sequence given above:
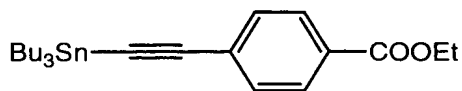
6b

10   For similar compounds where X = -C(CH₃)₂CH₂- , a similar synthetic

sequence may be employed, as shown in Scheme II:

15

20   Scheme II

23
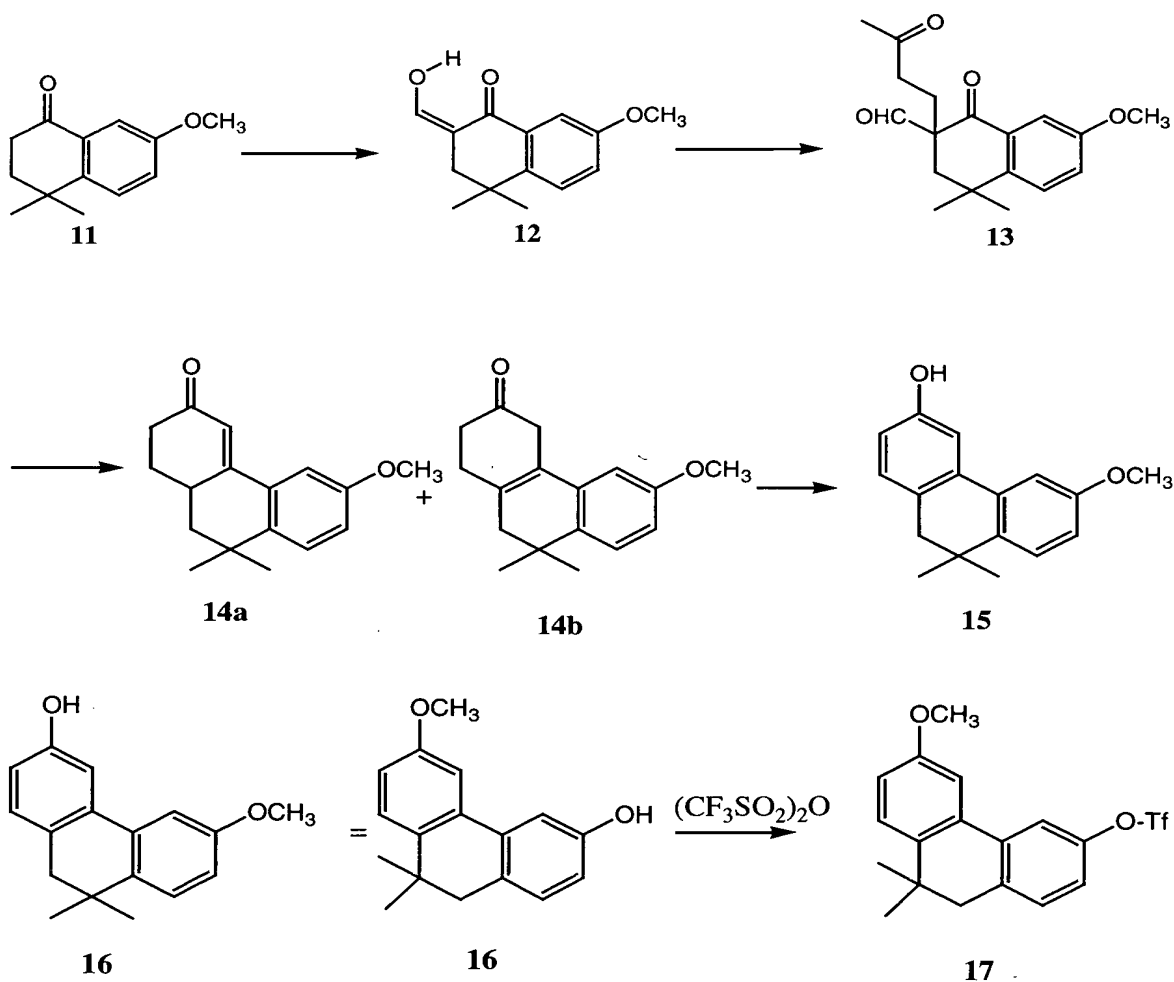
5

Starting from the known **11** (H. Hart et al; *J. Amer. Chem Soc.* 1963, *85*, 3269-3273), the sequence is carried out in the same fashion up to intermediate **16**, which can then be reacted with trifluoromethane sulfonic anhydride to produce the trifluoromethanesulfonate ("triflate", abbreviated "O-Tf"), **17,** which can then be

10 condensed with **6a** or **6b**, followed by hydrolysis of the ester, to give the corresponding final compound.

A more general route to general intermediates for compounds of the instant invention is shown diagrammatically in scheme III:

15
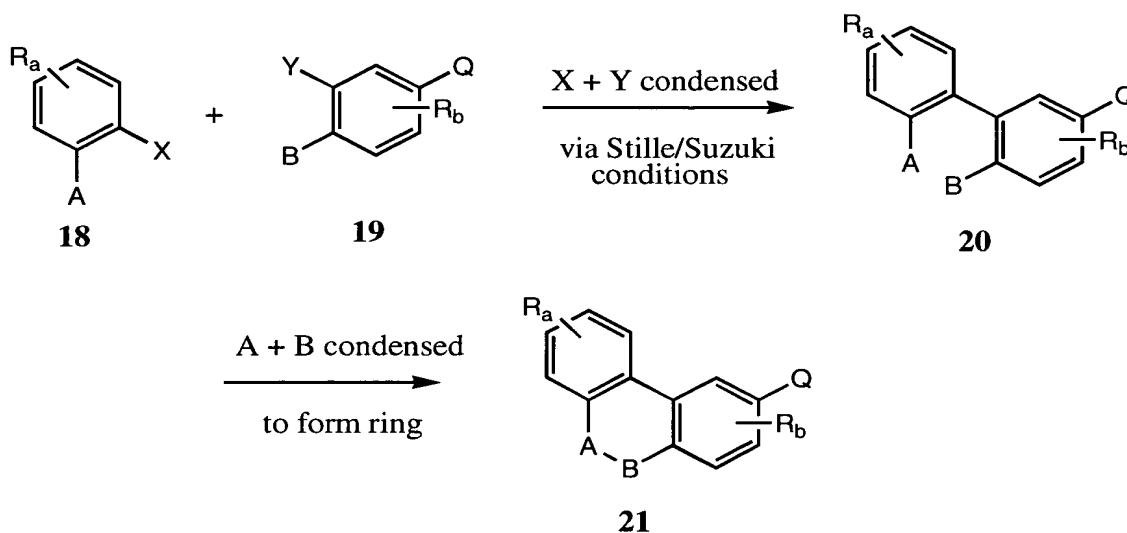
Scheme III

Monomeric intermediates **18** and **19**, where either of X or Y is halogen or

20 triflate and the other of X or Y is a stannane or borate functional group, may be condensed via metal catalysis, using a metal such as palladium, under Stille or Suzuki reaction conditions, to generate biphenyl intermediates **20**. Proper choices of A and B allow ring closure in a subsequent step, yielding intermediates 21, where the A-B linkage is equivalent to X in Formula I.

25 For X = -C(CH₃)₂CH₂-, A may be H and B may be HO-C(CH₃)₂CH₂-, and the ring closure may be done under acid or Friedel-Crafts catalysis, using, for example,

5   aluminum chloride as a catalyst. The functional group $HO-C(CH_3)_2CH_2-$ is available

using standard organic transformations from the corresponding methyl group

(compounds 22 are well-known in the literature):
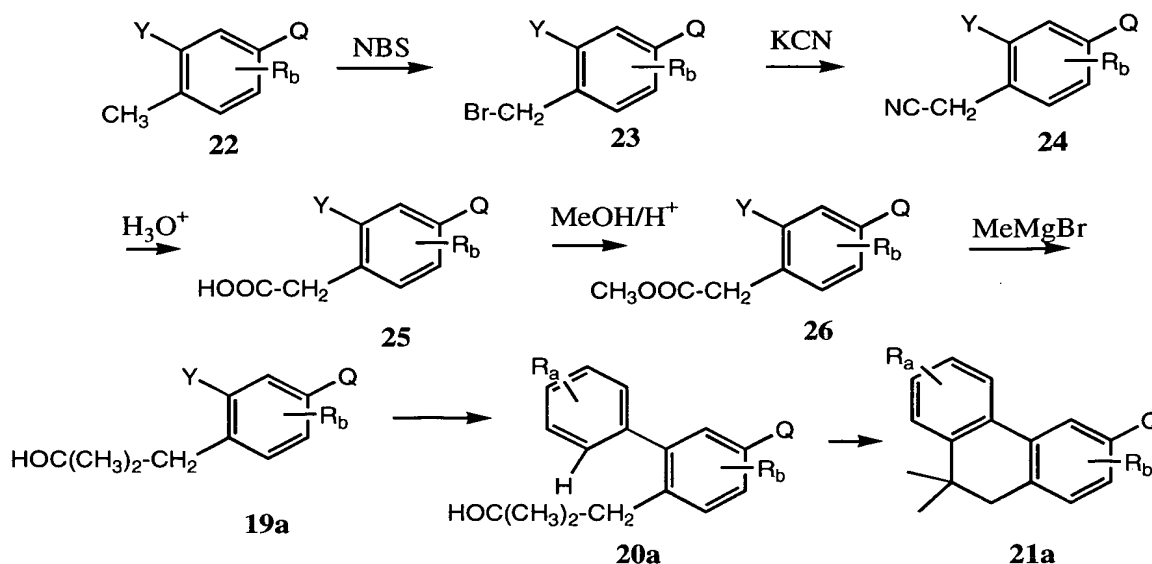
10

The methyl group of 22 is first brominated, using, for example, N-

bromosuccinimide ("NBS"), to give bromo-methyl intermediate 23. The bromine is

then replaced by a cyano group using, for example, potassium cyanide, to give 24.

The cyano group is then hydrolyzed to a carboxylic acid under standard conditions to

15   give 25, which may be esterified under standard conditions to give 26. The ester 26

may then be reacted with two equivalents of methylmagnesium bromide to give 19a,

which is then coupled with 18a (A = H) to give 20a, which is, in turn, cyclized under

acidic dehydrating conditions, using, for example, aluminum chloride, to give 21a.

In a similar fashion, for $X = - CH_2C(CH_3)_2-$, B will be H and A will be HO-

20   $C(CH_3)_2CH_2-$ to give the X group in reverse orientation. It may be necesssary to

separate the desired isomer 21a from the undesired regioisomer 22a in this case:

18a → **21a** + **22a**

5
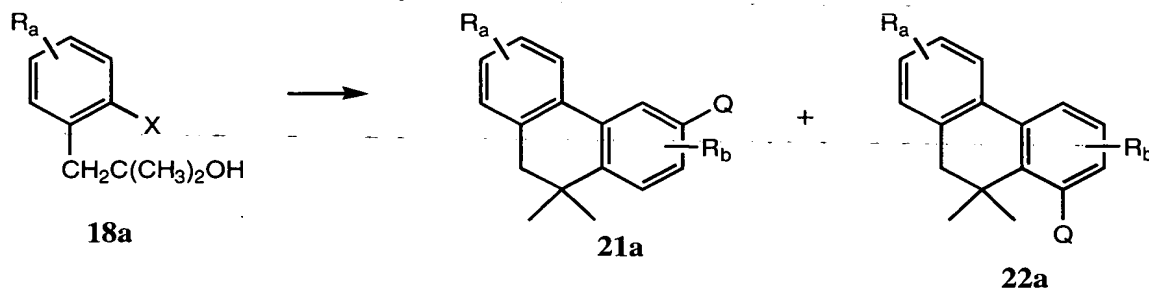
For X = -CH₂O- , A may be COOCH$_3$ and B may be OH (optionally protected with a suitable protecting group, designated "PG$_1$"). Following condensation of the appropriately substituted **18** and **19** to give biphenyl compound **20b**, the ester group is reduced to the corresponding alcohol, using, for example, a hydride reducing agent such as LiAlH$_4$, to give **27**. After removal of the phenol protecting group to give **28**, the alcohol and phenol groups may be condensed under, for example, Mitsunobu conditions, to give **21b**. A similar sequence may be used where A is OH (or O-PG$_1$) and B is COOCH$_3$ to give **21c** from **20c**, where X corresponds to -OCH$_2$-.

20b → **27** → **28** → **21b**

20c → **21c**

5
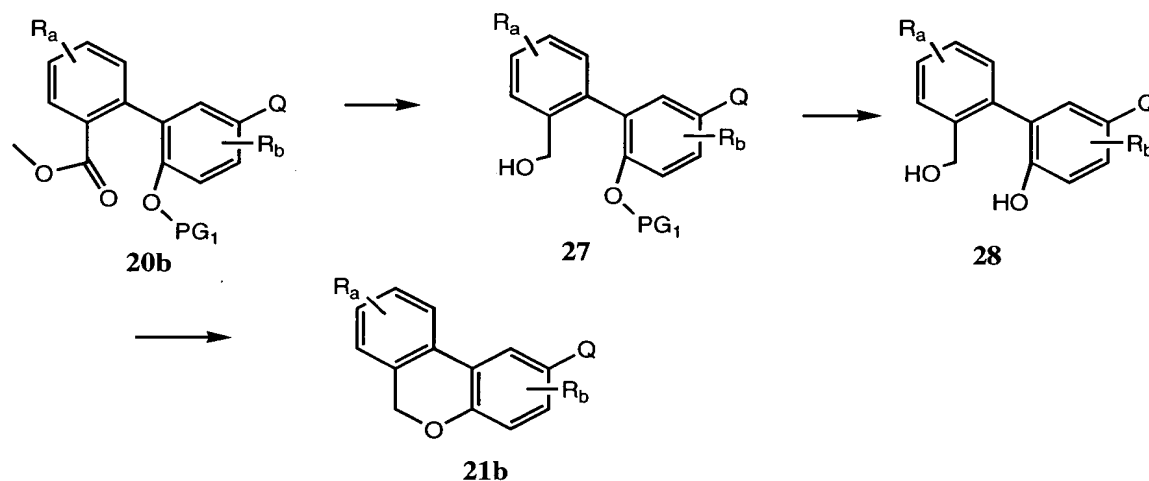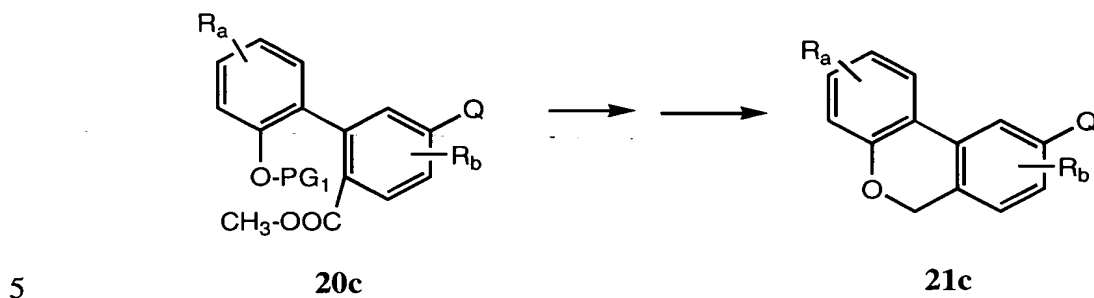
For X = -C(CH$_3$)$_2$O-, A may be COOH and B may be OH, and the following reaction sequence may be employed:


29 → **30** → **20d**

21d

10
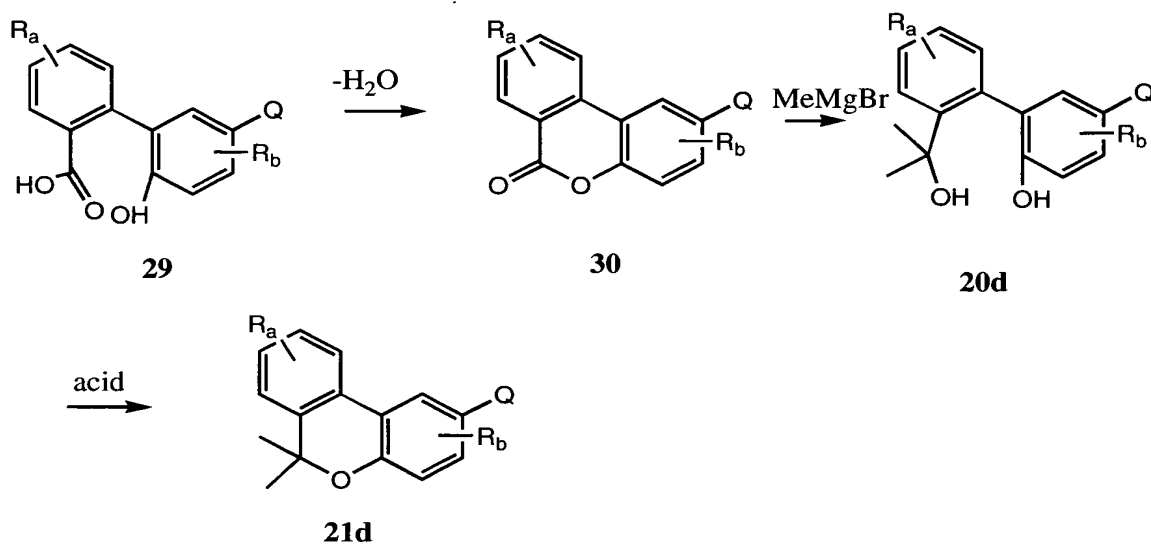
Intermediate **29** may be cyclized to lactone **30**, using a dehydrating agent, and then reacted with two equivalents of methyl magnesium bromide to give ring-opened diol **20d**. This compound may be re-cyclized under acid conditions to give **21d**.

15   Similarly, for **X** = -OC(CH$_3$)$_2$-, A may be OH and B may be COOH, and an equivalent reaction sequence employed to give **21e** from **31**.

31 → **21e**
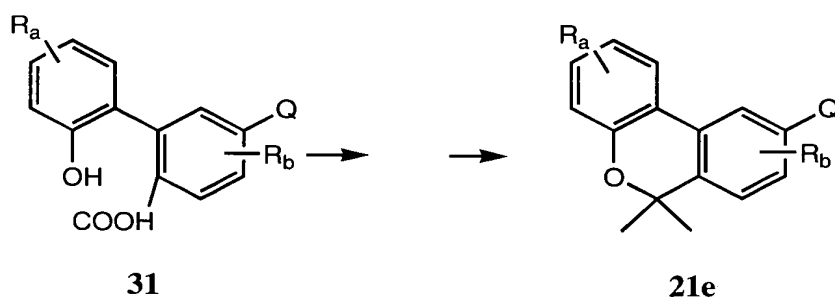
5

For **X** = -C(CH₃)₂S-, A may be COOH and B may be SH, and the following reaction sequence may be employed:

32   **33**   **20f**

21f
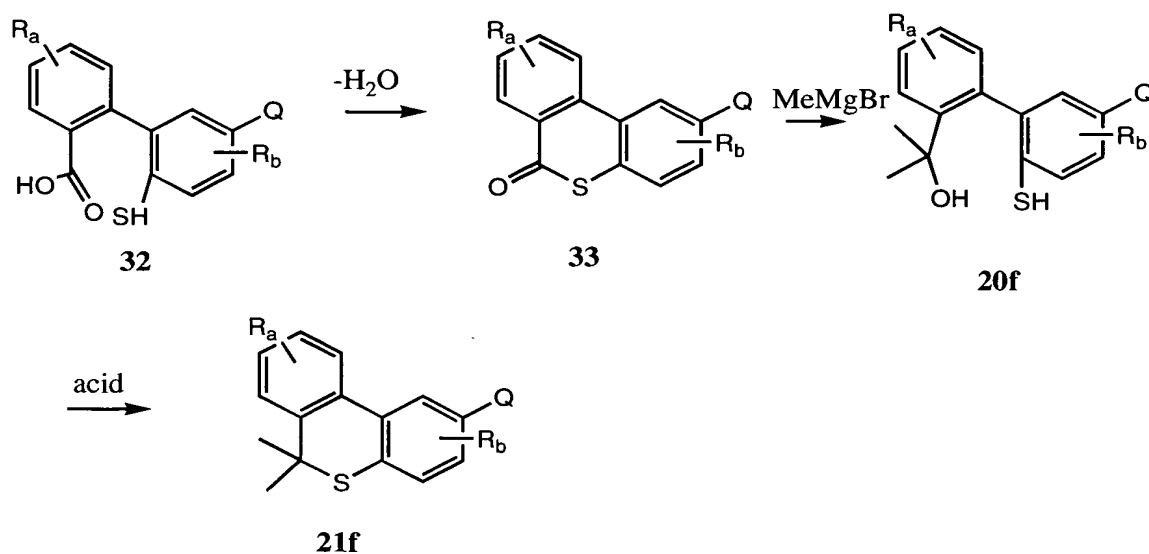
10

Intermediate **32** may be cyclized to thiolactone **33**, using a dehydrating agent, and then reacted with two equivalents of methyl magnesium bromide to give ring-opened alcohol/thiol **20f**, which may be re-cyclized under acid conditions to give **21f**.

Similarly, for X = -SC(CH₃)₂-, A may be SH and B may be COOH, and an

15   equivalent reaction sequence employed to give **21g** from **34**.

34   **21g**
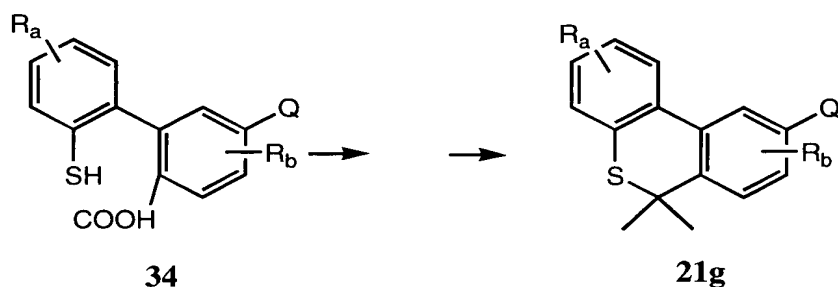
For X = -CH₂S-, A may be COOH and B may be SH, and the following reaction may be employed:

33

5

21h
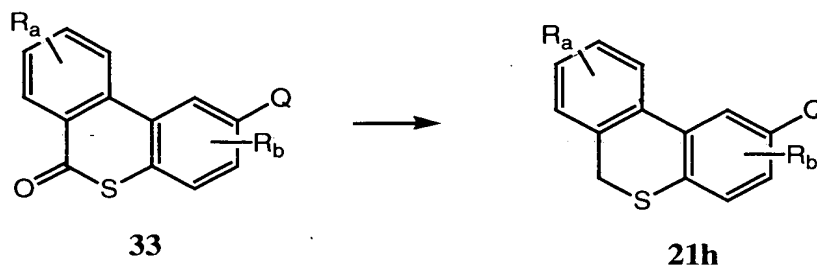
Intermediate **33**, may be reduced, using, for example, lithium aluminum hydride, to give compound **21h** directly. Alternatively, A may be CH_2OH and B may be SH, and the following reaction may be employed:

20h

10

21h
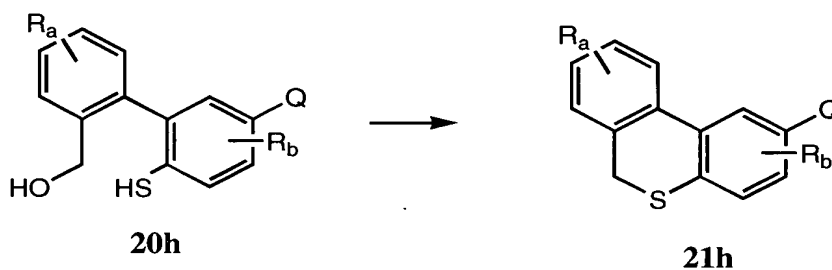
Compound **20h**, available from the reduction of **32**, may be cyclized using either acid or Mitsunobu-type conditions to give **21h**.
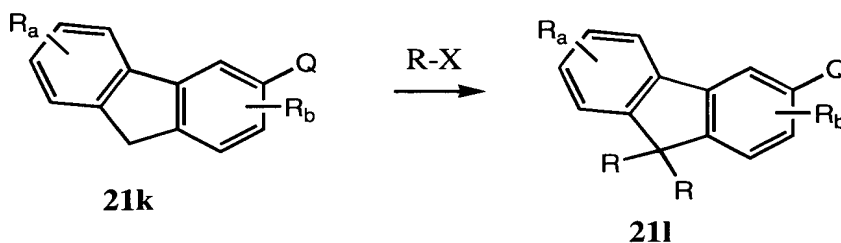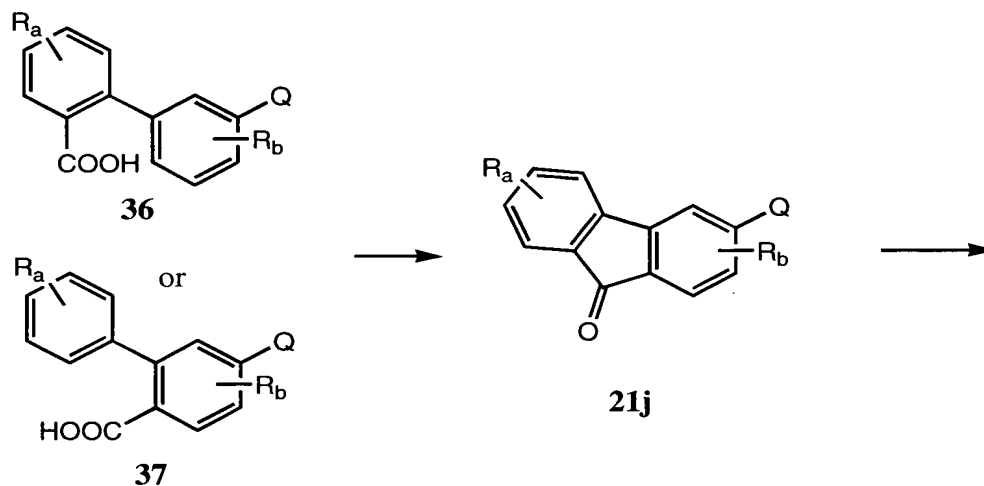
Similarly, for X = -SCH_2-, A may be SH and B may be COOH, and an

15 equivalent reaction employed to give **21i**, or A may be SH and B may be CH_2OH, as above:

35

21i

29

20i → **21i**
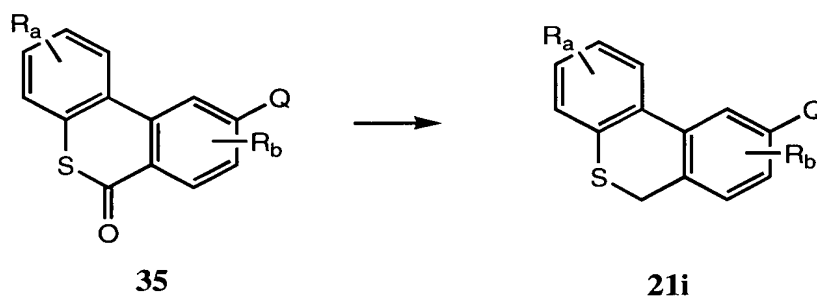
5
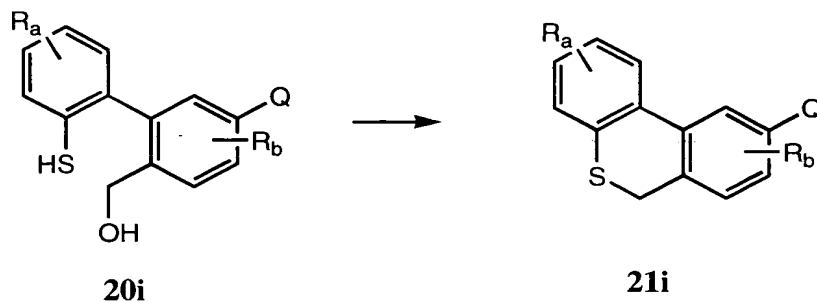
For X = C=O, CH₂, or C(R)₂, either of A or B may be COOH and the other of A or B is H. The following reaction sequence may be employed:


36

or

37

21j

21k →(R-X)→ **21l**

10

Either of acids **36** or **37** may be cyclized to give **21j** (X = C=O) under Friedel-Crafts or dehydrating acid conditions. It may be advantageous to use **37**, depending on the choice of R_a and R_b, to minimize the formation of positional isomers. The

15   ketone may be reduced under standard conditions to give **21k** (X = CH₂), and the

30

5   methylene group may be deprotonated using strong base followed by treatment with
an excess of alkyl halide, R-X, to give **21l,** X = C(R)$_2$.

For X = O, A and B may both be OH (intermediate **38**), and cyclization may
be effected using a reagent such as stannous chloride, or A and B may both be OCH$_3$
(intermediate **39**), and cyclization may be effected using a strong mineral acid such as
10   HBr, to give **21m:**
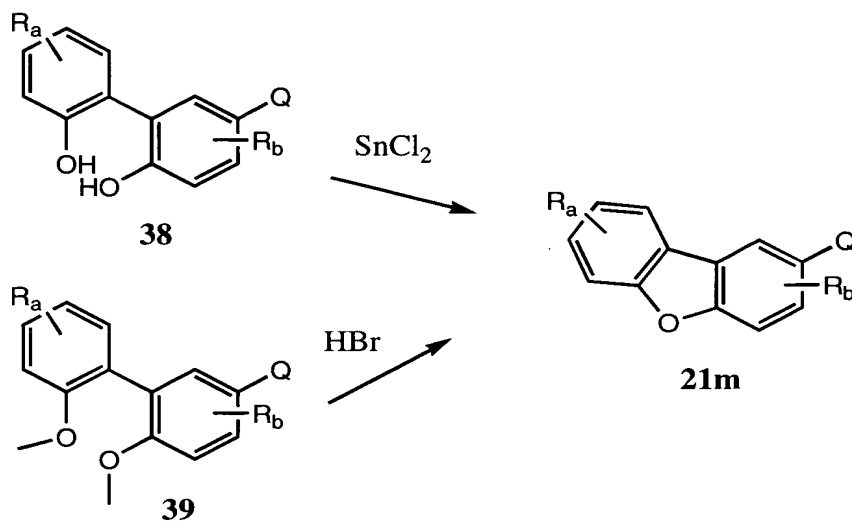
For X = S, one of A or B may be I and the other may be S-CH$_3$ (intermediate
15   **40**), and the cyclization may be carried out with a radical-generating agent such as
tributyl tin hydride to give intermediate **21n:**
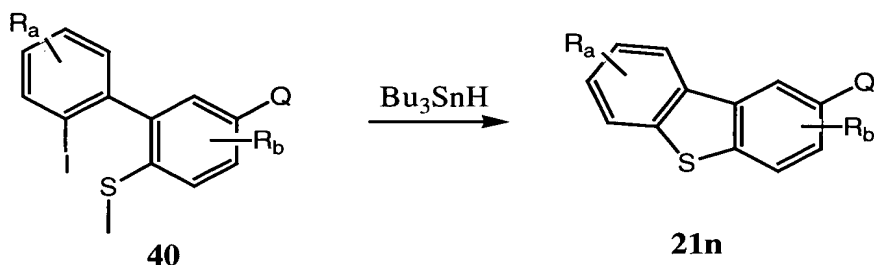
Intermediates **21(a-n)** may then be employed in the synthesis of a wide variety
20   of final products. For example, compounds **21** may be reacted with the known **41** to
give, after hydrolysis, final products **42a** (Linker = -CH=CH-) or with the known **43**
to give, after hydrolysis, final products **42b** (Linker = -C≡C-):

5

21   41   42a

43   42b
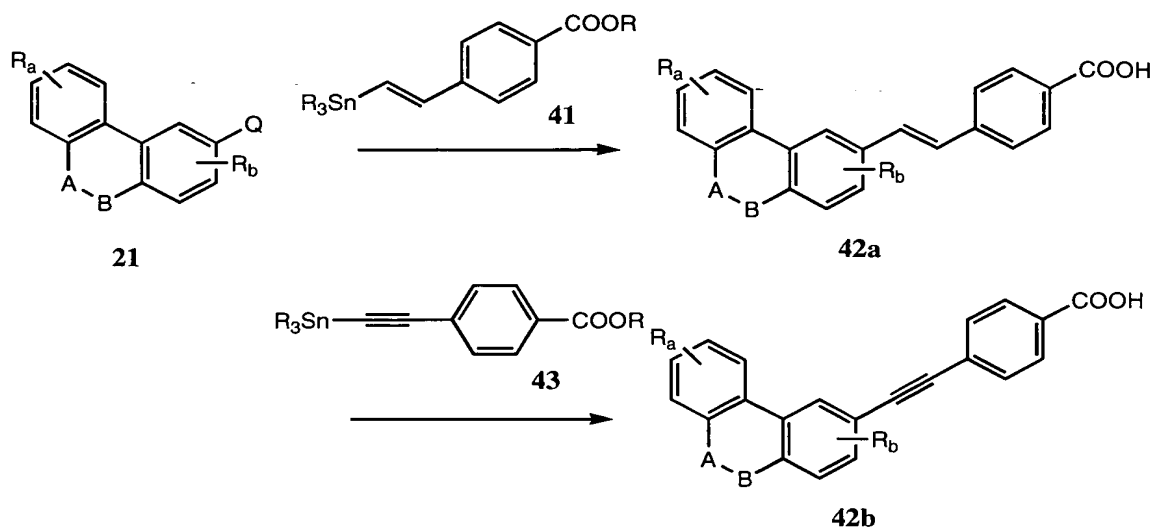
Alternatively, intermediates **21** may be carbonylated in the presence of carbon monoxide, palladium catalyst, and an alcohol, to give, after hydrolysis, acids **44**:
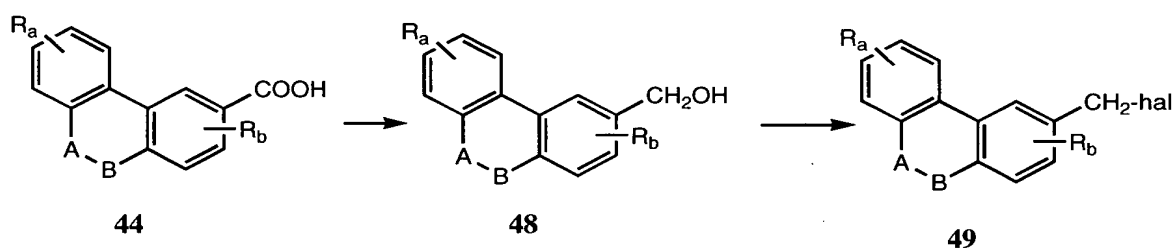
10

21   CO/Pd   H$_2$O   44
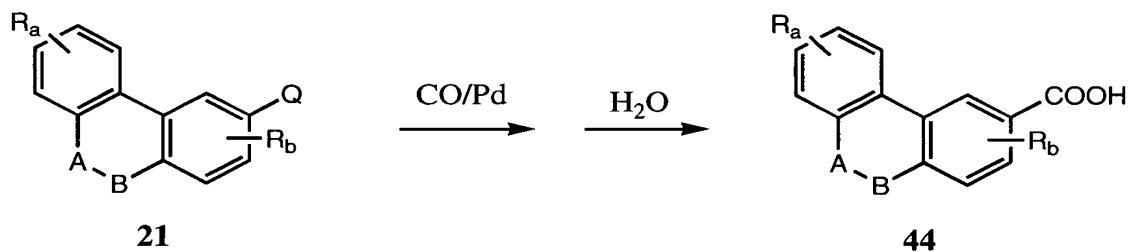
These acids may the be condensed with alkyl p-aminobenzoates **45**, to give, after ester hydrolysis, amides **42c**, with protected p-mercaptobenzoates **46** or protected p-hydroxybenzoates **47**, to give, after deprotection, thiolesters **42d** or esters

15   **42e**:
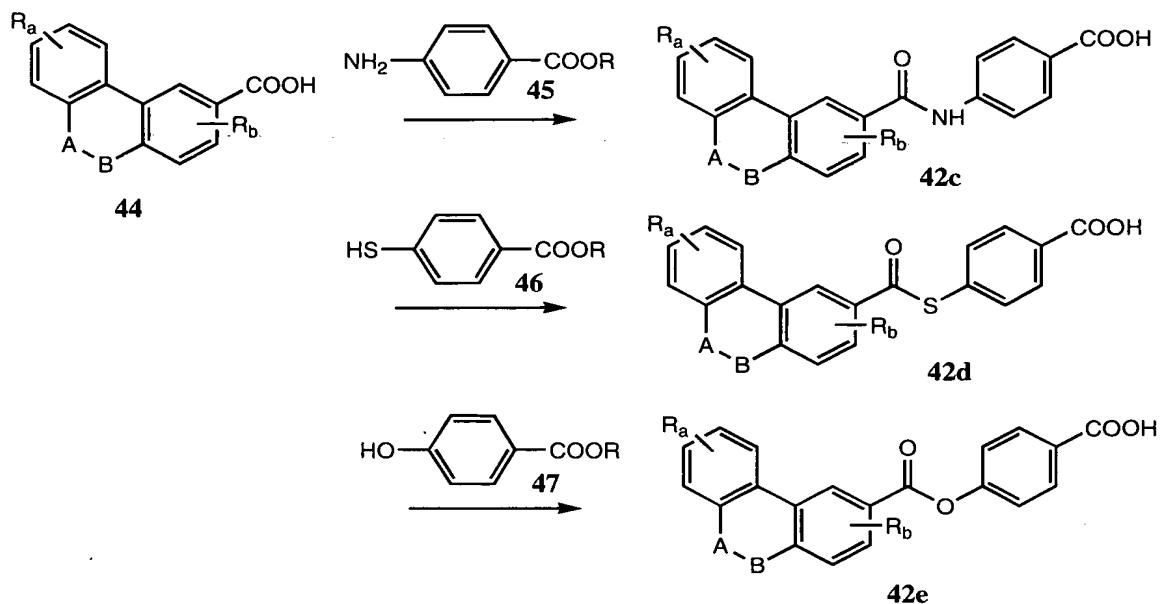
5   Alternatively, acids **44** may be reduced to alcohols **48**, which may then be converted to benzyl halides **49**:
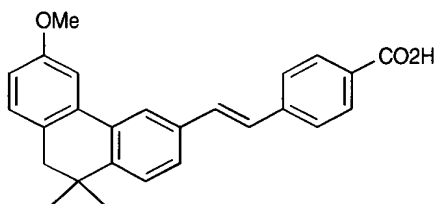

10

These benzyl halides **49** may then be reacted with alkyl p-aminobenzoates **45** to give, after ester hydrolysis, amines **42f**, with alkyl p-mercaptobenzoates **46** to give, after ester hydrolysis, thioethers **42g**, or with alkyl p-hydroxybenzoates **47** to give, after ester hydrolysis, ethers **42h**:
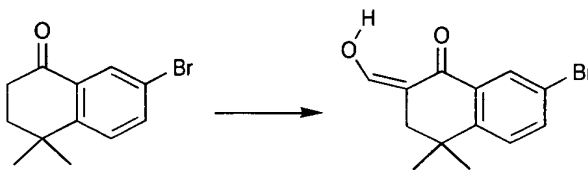
5
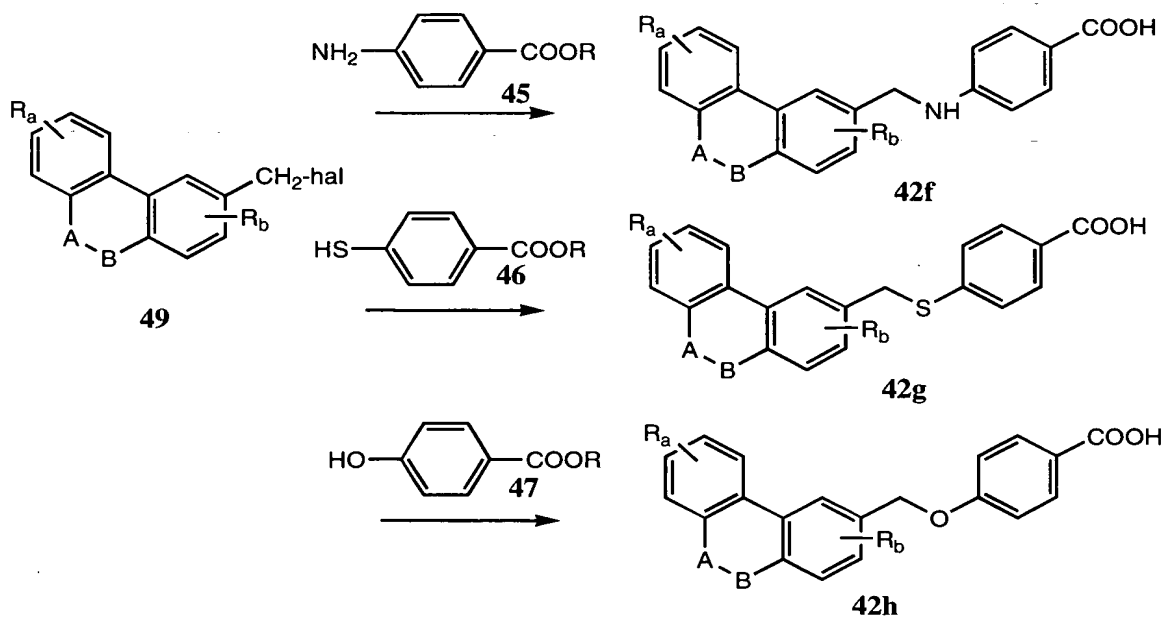
The following non-limiting examples serve to illustrate the practice of the invention.

10

Example 1

7-Bromo-4,4-dimethyl-2-formyl-1-oxo-1,2,3,4-tetrahydronaphthalene

15

34

5 A solution of 7-bromo-4,4-dimethyl-1-oxo-1,2,3,4-tetrahydronaphthalene (2.0 g, 7.9 mmol) in benzene (34 ml) was added to a cold (0°C) suspension of sodium hydride (60% in oil, 2.28 g, 57 mmol) and sodium methoxide (24 mgs) in benzene (34 ml). Ethyl formate (2.74 ml, 33.9 mmol) was then added dropwise and the mixture was stirred at 0°C for 2 hours and then at room temperature for 3 hours. Wet

10 methanol was then added and the aqueous phase was acidified with 4M hydrochloric acid and extracted with ethyl acetate (3x). The combined organic phases were washed with 2M sodium carbonate and the sodium carbonate phases were combined, acidified and reextracted with ethyl acetate. The combined organic phases were dried over anhydrous magnesium sulfate, concentrated and purified by silica gel chromatography
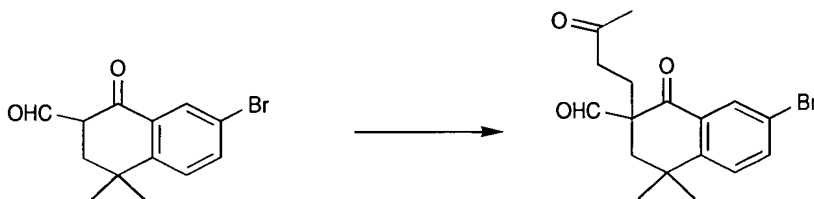
15 (ethyl acetate/hexane 10:90) to give the title material (2.1 g, 95%).

^{1}H NMR (CDCl$_3$, δ, ppm): 1.26 and 1.31 (2 x 3H, 2 s, 2 x -CH$_3$), 2.46 (2H, s, -CH$_2$-6), 7.27 (1H, d, H-4), 7.60 (1H, dd, J=8.4 and 2.0 Hz, H-3), 8.10 (1H, d, J=2.0 Hz, H-1), 8.19 (1H, s, =CH-OH), 14.4 (1H, s, -OH).

20 Example 2

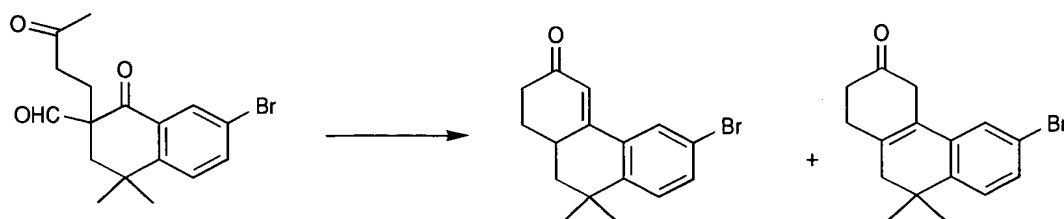7-Bromo-4,4-dimethyl-2-formyl-2-(3-oxo-butyl)-1-oxo-1,2,3,4-tetrahydronaphthalene

7-Bromo-4,4-dimethyl-2-formyl-1-oxo-1,2,3,4-tetrahydronaphthalene (1.0 g,

25 3.56 mmol) was dissoved in methylvinylketone (dist., 0.468 g, 6.7 mmol) and this mixture was cooled down to 0°C. Triethylamine (3 drops) was then added and the mixture was stirred at 0°C for an hour and then at room temperature overnight. The reaction mixture was dissolved in ethyl ether and concentrated to give the title material (1.09 g, 87%) as a yellow oil.

30 ^{1}H NMR (CDCl$_3$, δ, ppm):1.08 and 1.46 (2 x 3H, 2 s, 2 x -CH$_3$), 1.86 (1H, d, J=14.2 Hz, H-6), 2.04-2.10 (2H, m, -CH$_2$-), 2.12 (3H, s, -COCH$_3$), 2.35-2.50 (2H, m, -

5 CH₂CO-), 2.53 (1H, d, J=14.2 Hz, H-6), 7.27 (1H, d overlapped by CDCl₃, H-4), 7.66

(1H, dd, J=8.4 and 2.3 Hz, H-3), 8.07 (1H, d, J=2.2 Hz, H-1), 9.82 (1H, s, -CHO).

Example 3

6-Bromo-9,9-dimethyl-3-oxo-1,2,3,9,10,10a-hexahydrophenanthrene

10

A solution of 7-bromo-4,4-dimethyl-2-formyl-2-(3-oxo-butyl)-1-oxo-1,2,3,4-
tetrahydronaphthalene (1.71 g, 4.87 mmol) in methanol (170 ml) was treated with a
solution of lithium hydroxide hydrate (0.854 g, 20.35 mmol) in water (85 ml) . the
reaction was stirred at room temperature for 45 minutes and then the temperature was
15 raised to 50°C and the mixture was stirred for another 2 hours. The reaction was
quenched with water and adjusted to pH 5 with 4M hydrochloric acid. The aqueous
phases were extracted with ethylacetate (3x) and the combined organic phases were
washed with water and dried over anhydrous magnesium sulfate. The residue was
purified by silica gel chromatography (hexane/ethylacetate 95:5 to 90:10) to give the
20 title material (0.631 g, 42%) along with 6-bromo-9,9-dimethyl-3-oxo-1,2,3,4,9,10-
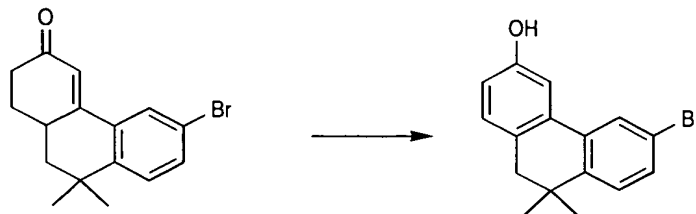hexahydrophenanthrene (0.371 g, 25%).

¹H NMR (CDCl₃, δ, ppm): 1.25 and 1.35 (2 x 3H, 2 s, 2 x –CH₃), 1.71-1.82 (2H, m, -
CH₂-), 2.14-2.20 (1H, m, -CH₂-), 2.41-2.50 (1H, m, -CH₂-), 2.55-2.60 (1H, m, -CH₂-),
2.78-2.86 (1H, m, -CH₂-), 6.55 (1H, d, J=1.9 Hz, H-4), 7.30 (1H, d, J=8.5 Hz, H-8),
25 7.48 (1H, dd, J=8.5 and 2.0 Hz, H-7), 7.83 (1H, d, J=2.0 Hz, H-5).

36

5

Example 4

6-Bromo-9,9-dimethyl-3-hydroxy-9,10-dihydrophenanthrene


10   6-Bromo-9,9-dimethyl-3-oxo-1,2,3,9,10,10a-hexahydrophenanthrene (0.250 g, 0.819 mmol)), palladium(II) dichloride (0.190 g, 10.7 mmol) and tert-butanol (5 ml) were mixed in a sealed tube and heater to 125-135°C for 4 hours. The reaction is finished when all the palladium has precipitated on the glass wall and a yellow and transparent reaction mixture is observed. Water was then added and the aqueous phase was extracted with ethyl acetate. The organic extracts were dried with

15   anhydrous magnesium sulfate and concentrated. The residue was purified by silica gel chromatography (ethyl acetate/hexane 5:95 to 10:90) to give the title material (0.225 g, 91%).

^{1}H NMR (CDCl$_3$, δ, ppm): 1.22 (6H, s, 2 x -CH$_3$), 2.68 (2H, s, -CH$_2$-10), 6.74 (1H, dd, J=8.1 and 2.5 Hz, H-7), 7.06 (1H, d, J=8.1 Hz, H-8), 7.18 (1H, d, J=2.5 Hz, H-5),

20   7.27 (1H, d overlapped by CDCl$_3$, H-1), 7.39 (1H, dd, J=8.2 and 2.0 Hz, H-2), 7.80 (1H, d, J=2.0 Hz, H-4).

Example 5

a.) 4-(2-Tributylstannyl-vinyl)-benzoic acid, methyl ester

25
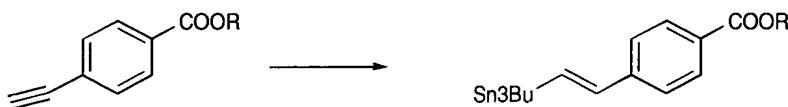
5   500 mg (3.1 mmol) 4-ethynyl-benzoic acid methyl ester, 1.3 ml (1.4 g; 4.8

mmol) tributyltin hydride and 50 mg (0.3 mmol) AIBN [1,1'-azobis(isobutyronitrile)]

were dissolved in 5 ml benzene and refluxed for 2 hours. The reaction mixture was

then cooled to room temperature, the solvent was removed under reduced pressure,

and the residue was columned through silica using 1% Et$_3$N in 5% EtOAc/hexane to

10   afford 1.35 g (96%) product as a light yellow oil.

^{1}H NMR (300 MHz, CDCl$_3$): 0.8-1.1 (m, 15H), 1.2-1.5 (m, 6H), 1.5-1.7 (m, 6H),

3.93 (s, 3H), 6.92 (d, 2H, 19.5 Hz), 7.08 (d, 2H, J=19.5 Hz), 7.48 (d, 2H, J=8.4 Hz),

8.00 (d, 2H, J=8.4 Hz); IR: cm^{-1}; MS (DCI): 451 (M+H)$^+$

15   b.) 4-(2-Tributylstannyl-vinyl)-benzoic acid, ethyl ester

          The title compound was prepared similarly to the methyl ester:

A solution of ethyl 4-ethynylbenzoate (3.16 g, 18.1 mmol) in toluene (25 mL) was

treated with 2,2'-azobisisobutyronitrile (AIBN) (0.300 g, 1.83 mmol) and tributyltin

20   hydride (7.3 mL, 27.1 mmol). The mixture was heated to 90°C for 1.5 hours. After

cooling to room temperature, the solvent was evaporated and the residue was purified

on silica gel (2% ethyl acetate/hexane + 1% triethylamine) to give the title material

(6.54 g, 78%) as a yellow oil.

25   c.) Ethyl 4-[2-(E)-[10,9-dihydro-9,9-dimethyl-3-hydroxy]-6-

phenanthrenyl]ethenyl]benzoate
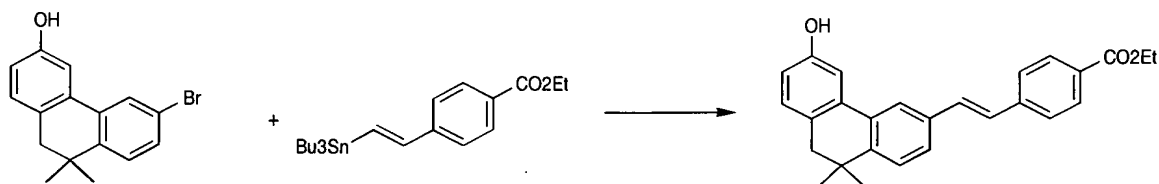
30

          A solution of 6-bromo-9,9-dimethyl-3-hydroxy-9,10-dihydrophenanthrene

(0.085 g, 0.28 mmol), ethyl 4-((2-tributylstannyl)ethenyl)benzoate (0.190 g, 0.408

mmol) and tetrakistriphenylphosphinepalladium(0) (28 mg) in toluene (5 ml) was

5 heated to 100-105°C for 6 hours. Water was added and the aqueous phase was
extracted with ethyl acetate. The combined organic extracts were dried over
anhydrous magnesium sulfate, filtered and concentrated. The residue was purified by
silica gel chromatography (ethyl acetate/hexane 10:90 to 20:80) to give the title
material.

10 ^{1}H NMR (CDCl$_3$, δ, ppm): 1.26 (6H, s, 2 x -CH$_3$), 1.41 (3H, t, J=7.1 Hz, -CH$_3$), 2.71
(2H, s, -CH$_2$-10), 4.40 (2H, qa, J=7.1 Hz, -OCH$_2$-), 6.76 (1H, dd, J=8.0 and 2.5 Hz,
H-7'), 7.08 (1H, d, J=8.1 Hz, H-8'), 7.14 and 7.23 (2 x 1H, 2d, J$_{AB}$=16.3 Hz, vinyl H),
7.34 (1H, d, J=2.5 Hz, H-5'), 7.41 (1H, d, J=8.1 Hz, H-1'), 7.46 (1H, dd, J=8.1 Hz 1.3
Hz, H-2'), 7.57 (2H, d, J=8.2 Hz, H-3 and H-5), 7.84 (1H, br s, H-4'), 8.05 (2H, d,
15 J=8.3 Hz, H-2 and H-6).

Example 6
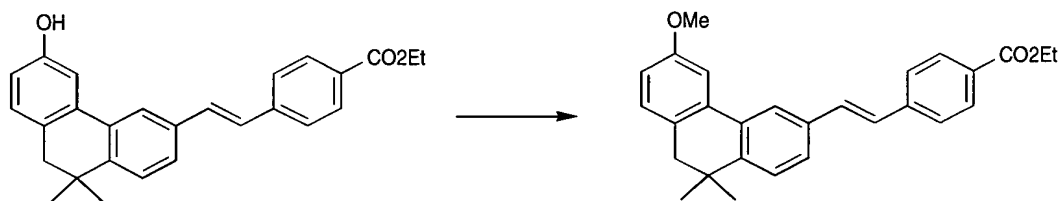
20

Ethyl 4-[2-(E)-[10,9-dihydro-9,9-dimethyl-3-methoxy]-6-
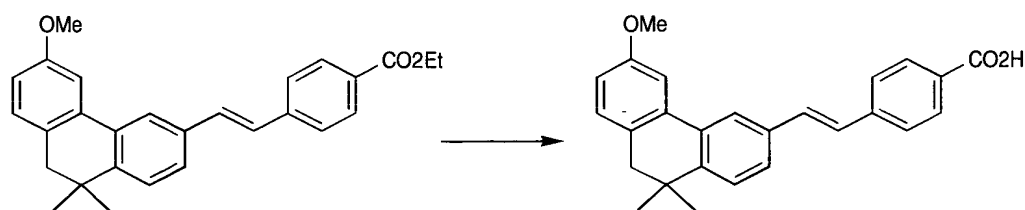phenanthrenyl]ethenyl]benzoate

A solution of ethyl 4-[2-(E)-[10,9-dihydro-9,9-dimethyl-3-hydroxy]-6-
25 phenanthrenyl]ethenyl]benzoate (0.074g, 0.19 mmol) in acetone (5 ml) was treated
with potassium carbonate (0.077g, 0.56 mmol) and iodomethane (50 μl, 0.80 mmol).
The mixture was heated under reflux for 3 hours and treated again with potassium
carbonate (0.090g, 0.65 mmol) and iodomethane (500 μl, 8.0 mmol). The mixture
was heated again under reflux for 5 additional hours in adding enough iodomethane to
30 complete the reaction. The mixture was cooled down to room temperature and
filtered and the solvent was evaporated. The residue (0.151g) was purified on TLC
plates (15% ethyl acetate/hexane) and gave the title material (0.045g, 57%).

39

5   ^{1}H NMR (DMSO-d$_6$, δ, ppm): 8.12 (1H, s, H-4'), 7.98 (2H, d, J=8.8 Hz, H-2 and H-
6), 7.77 (2H, d, J=8.8 Hz, H-3 and H-5), 7.60 (1H, dd, J=8.1 Hz, H-2'), 7.52-7.45 (4H,
m, H-5', H-1' and vinyl H), 7.18 (1H, d, J=8.8 Hz, H-8'), 6.87 (1H, dd, H-7'), 4.33
(2H, qa, J=7.3 Hz, -CH$_2$O-), 3.85 (3H, s, -OMe), 2.69 (2H, s, -CH$_2$-10), 1.34 (3H, t,
J=7.3 Hz, -CH$_3$), 1.20 (6H, s, 2 x -CH$_3$).

10   MS (ESI): 413.10 (M+H)$^+$

Example 7

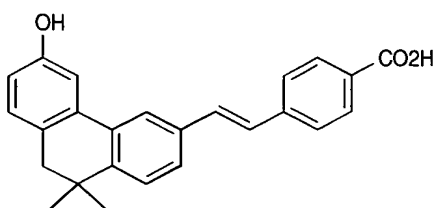4-[2-(E)-[10,9-Dihydro-9,9-dimethyl-3-methoxy]-6-phenanthrenyl]ethenyl]benzoic
acid

15

A solution of ethyl 4-[2-(E)-[10,9-dihydro-9,9-dimethyl-3-methoxy]-6-
phenanthrenyl]ethenyl]benzoate (0.037g, 0.090 mmol) was degassed with argon and
then treated with NaOH (5N, 70µl, 0.35 mmol). The mixture was stirred at room
20   temperature for 20 hours. NaOH (5N, 100 µl, 0.5 mmol) was added again and the
reaction was stirred for 6 additional hours. The mixture was diluted with ethyl acetate
(25 ml) and poured into a solution of 1N HCl (20 ml). The organic phases were
separated and the aqueous phase was extracted with ethylacetate (2 x 5 ml). The
combined organic extracts were washed with water and brine, dried over anhydrous
25   magnesium sulfate, filtered and concentrated. The residue was dissolved into a
mixture of ethyl ether/dichloromethane and hexane was added. The solution was
concentrated under vacuum and the solid was filtered. The solid was dissolved in
methanol, ethanol and ethyl ether. The solution was filtered on a fiber glass paper and
evaporated. Water was added to the residue and the product was lyophilized to give
30   the title material (compound **10**)as a white solid.

5   ^{1}H NMR (DMSO-d$_6$, δ, ppm): 8.12 (1H, s, H-4'), 7.98 (2H, d, J=8.8 Hz, H-2 and H-
6), 7.77 (2H, d, J=8.8 Hz, H-3 and H-5), 7.60 (1H, dd, J=8.1 Hz, H-2'), 7.52 (1H, d,
H-5'), 7.47 (2H, s, vinyl H), 7.46 (1H, d, J=8.1 Hz, H-1'), 7.18 (1H, d, J=8.1 Hz, H-8'),
6.87 (1H, dd, J=8.1 and 2.1 Hz, H-7'), 3.85 (3H, s, -OMe), 2.69 (2H, s, -CH$_2$-10), 1.20
(6H, s, 2 x -CH$_3$). MS (ESI): 383.07 (M-H)$^-$. HRMS for C$_{26}$H$_{23}$O$_3$ Calcd: 383.16473

10   Found: 383.16320

Example 8

15   4-[2-(E)-[10,9-Dihydro-9,9-dimethyl-3-hydroxy]-6-phenanthrenyl]ethenyl]benzoic
acid

A solution of ethyl 4-[2-(E)-[10,9-dihydro-9,9-dimethyl-3-hydroxy]-6-
phenanthrenyl]ethenyl]benzoate (0.040 g, 0.10 mmol) in tetrahydrofuran (1.5 ml) and

20   ethanol (1.5 ml) was treated with an aqueous solution of sodium hydroxide (5M,
0.142 ml, 0.71 mmol) and the reaction was stirred overnight. The reaction was then
diluted with water (~10 ml) and acidified by the addition of aqueous HCl (4M). The
precipitated product was filtered and washed with water. The residual solid was
purified by Prep HPLC and afforded the title material (compound 8) (18 mgs, 49%) as

25   a white fluffy solid.

^{1}H NMR (DMSO-d$_6$, δ, ppm): 1.20 (6H, s, 2 x -CH$_3$), 2.64 (2H, s, -CH$_2$-10'), 6.71
(1H, d, J=8.0 Hz, H-1' or H-8'), 7.05 (1H, d, J=8.1 Hz, H-1' or H-8'), 7.34 (1H, s, H-
5'), 7.40-7.51 (3H, m, vinyl H and H-7'), 7.58 (1H, d, J=8.0 Hz, H-2'), 7.75 (2H, d,
J=8.0 Hz, H-3 and H-5), 7.94 (1H, s, H-4'), 7.97 (2H, d, J=8.0 Hz, H-2 and H-6), 9.29

30   (1H, s, -OH), 12.89 (1H, s, -CO$_2$H).

IR ν (cm^{-1}): 3401, 3188, 2961, 1685 (C=O) and 1602.

41

5   Example 9

Assay methodology (retinoic acid is used as a positive control in all assays):

Competition Binding Assay using Yttrium SPA Beads

10   Principle of the assay: The Yttrium SPA beads have the property of binding to
the His-tag-fused Ligand Binding Domain (LBD) of RARα, β and γ iso-types. The
binding of a tritiated RAR-ligand ($[^3H]$-tRA) to the RAR LBD will stimulate the SPA
bead creating an emission of fluorescence measured in a scintillation top count
counter.

15   Protocol: His-RARα, β or γ were over-expressed in *E. coli* BL21 (DE3) strain
according to the protocol described by Rochel et al. (Rochel et al., 1997, Biochem.
Biophys. Res. Com. 230, 293-297). The competition binding assay was performed in
96 well opti-plates (Packard) in Tris-HCl 20mM pH 8, NaCl 100mM, BSA 0.5% and
in a final volume of 80μl. In this order was added, 10μl of His-RARα, β or γ (the
20   quantity of protein added in the assay was primarily defined by titration), 50μl of 8
times diluted Ytrium SPA beads, 10μl of increasing concentrations of competitor
ranging from 0.1nM to 10μM and 10μl of a saturating concentration (5nM) of [3H]-
all trans Retinoic Acid (NEN life Sciences). The non-specific binding of the
radioligand was determined in the presence of 500-fold excess of cold *all-trans*
25   Retinoic Acid. The plates were incubated 2h at 4°C under gentle shaking and counted
in a top count scintillation counter (Packard). Binding data are reported as apparent
Kd's, in nM

Transactivation Assay

30   The transactivation assay measures the ability of a retinoid to activate a
reporter gene in the presence of one of the retinoic acid receptor subtypes (.alpha.,
.beta., or .gamma.). Activation of just one receptor and failure to activate another is
the basis for selectivity/specificity. In our definitions, "selectivity" means that the
compound preferentially activates one receptor but also activates at least one other at
35   a higher concentration and "specificity" means that the compound activates only one

5   receptor in the concentration range tested. The details of the receptor-based

transactivation assay are disclosed in the literature, e.g. see Nature 1988, 332, 85C-

853.

Principle of the assay: The agonistic, antagonistic or mixed agonist/antagonist

activity of the compound was determined in stable HeLa cell lines which are

10   expressing the chimerical receptors, GAL-RARα, β or γ along with the (17mer) x5-

Glob-Luc reporter gene. The chimerical receptors GAL-RARs were the result of the

fusion between the DNA Binding Domain of the yeast transcription factor GAL4 and

the LBDs of RARα, β or γ. The reporter gene contains the Luciferase coding

sequence downstream to the minimal promoter of the Globine gene, all together under

15   the control of 5 repeats of the GAL4 DBD response element, 17mer. The culture of

the cells in the presence of increasing concentration of compound ranging from 1pM

to 1μM will define the agonistic potential of the ligand. Inversely, incubation of the

cells with a saturating concentration of *all trans* Retinoic (10nM) giving 100% of

activation and in the presence of the same range of the compound concentrations

20   (1pM to 1μM) will characterize any antagonistic potential of the retinoid.

Protocol: 1.5×10^4 cells are plated per well of 96 well plates and let adhering

overnight to the support. The next day, the ligands are added and incubated for 24

hours. The expression of the Luciferase is measured by using the "Luc Lite" kit from

Packard according to the recommendations of the manufacturer. Transactivation data

25   are reported as EC_{50}'s in nM

Growth Assay

Principle of the assay: The proliferation of the cells was measured by the

incorporation of [^{3}H]-Thymidine in the DNA of dividing cells.

30   Protocol: The number of cells which was plated has been primarily defined to

avoid the cells reaching confluence before the end of the experiment duration (T47D

& HT3, 750cells/well; H3396, 200cells/well of 96 well plates). The first day, the cells

were plated in 96 well plates and incubated overnight at 37°C (in O_2, 95%; CO_2, 5%),

allowing the cells adhering to the support. The next day, the compounds were added

35   to the cells and incubated for 3 or 6 days (note: for the 6-day incubation, the medium

was replaced at Day3). At the end of the treatment, 10μl of [^{3}H]-thymidine (final

5 concentration of 0.4μCi/well) were added for 4 hours at 37°C, the medium was finally removed, the cells trypsinized and harvested under vacuum on GF/B glass fiber filters. After 3 washes with distilled water, the filter were dried and counted in a scintillation counter after adding 50μl of Microscint (Packard) to each filter. The percentage of growth inhibition was calculated by using DMSO as reference, which is

10 the vehicle of the compounds. Growth inhibition is reported as IC_{50}'s in nM

The structures and data for compounds **8** and **10** are shown below:
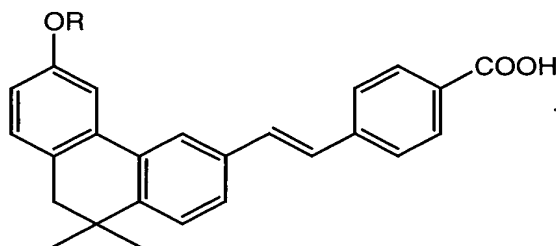
Compound **8**, R = H
Compound **10**, R = CH_3

Compound	Binding (Kd, nM)			Transactivation (EC_{50}, nM)			Cell Growth Inhibition (IC_{50}, nM)	
	RARα	RARβ	RARγ	RARα	RARβ	RARγ	T47D	HT3
8	8.3	18.6	52.8	13.5	1.76	47	4.8	1161
10	1.1	1.6	10.6	0.02	0.005	1.9	< 0.01	< 0.01
Retinoic acid	2.4	1.6	1.0	0.4	0.08	0.1	6.5	1

15

As can be seen from the table above, compounds **8** and **10** are both active in all three assay systems, with compound **10** being the more active. Its binding and transactivation properties compare very favorably with those of the highly active natural ligand, retinoic acid, being essentially the same for the RARα and RARβ

20 receptor, with some decrease in activity at the RARγ receptor. However, it has significantly enhanced inhibition against the two tested cell lines. Without wishing to

5   be bound by any particular theory, it is believed that compounds **8** and **10** may be more stable metabolically than the relatively labile retinoic acid, and that their greater persistence is the cause of their greater activity.